Benzylpenicilloyl Polylysine (Pre-Pen)

National Drug Monograph

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VA Pharmacy Benefits Management Services,
Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary:

Description:

- Benzylpenicilloyl polylysine (Pre-Pen) is a skin-test reagent, which has been reintroduced to the market as a diagnostic tool to aid providers in determining if a patient, based on previous experience of developing a reaction to penicillin, will be able to utilize penicillin antibiotic therapy.
- Benzylpenicilloyl polylysine was FDA approved in 2009 for the assessment of sensitization to penicillin (benzylpenicillin or penicillin G) in those patients suspected of having a clinical hypersensitivity to penicillin.
- Benzylpenicilloyl polylysine is the major determinant of an IgE mediated penicillin allergy.
- Roughly 10% of patients who report a severe allergic reaction to penicillin will remain intolerant their entire lives, the remaining will stop expressing the penicillin specific IgE (through time) and can be safely treated with penicillin.

Efficacy:

- The use of benzylpenicilloyl polylysine can detect between 75-90% of all positive reactions to penicillin.
- Experts recommend skin testing for penicillin hypersensitivity with both benzylpenicilloyl polylysine (Pre-Pen, major determinant) and penicillin G (a minor determinant) diluted with saline to a concentration of 10,000 units/ml. The addition of skin testing with penicillin G improves identification of patients with IgE mediated penicillin allergy with up to 97% of patients identified.
- Skin testing should also involve a positive control (commercial histamine 1 mg/ml for intradermal skin testing) and a negative control (usually saline, or allergen diluent).
- Patients who have had a previous hypersensitivity to penicillin have shown a higher positivity rate to benzylpenicilloyl polylysine than those who have had no such reactions following previous therapy with penicillin.
- A negative skin test to benzylpenicilloyl polylysine is associated with an incidence of immediate allergic reactions of less than 5% after the administration of therapeutic penicillin.
- The incidence of an immediate allergic reaction may be more than 50% in those patients with a positive skin test reaction to benzylpenicilloyl polylysine after use of therapeutic penicillin.
- Whether a negative benzylpenicilloyl polylysine skin test will predict a lower risk of anaphylaxis is not known.

Safety:

- There is a risk of developing a systemic allergic reaction (with potential for anaphylaxis) to benzylpenicilloyl polylysine.
- To reduce the risk of a systemic allergic reaction, puncture/prick skin testing should be conducted first and intradermal skin testing performed only after the puncture test is entirely negative.
- No deaths were reported from the use of benzylpenicilloyl polylysine
- Because of the risk for systemic allergic reactions, skin testing should be performed in an appropriate healthcare setting with direct medical supervision.

Dosing:

- Skin testing should be performed in a two-step manner:

Step 1) Puncture or prick test (inner volar aspect of the forearm): Using a 22-28-gauge needle, apply a small drop of skin test antigen to the test site, then puncture the epidermis using the same needle, do not draw any blood. Using separate needles, follow the same procedure for applying penicillin minor determinant mixture (MDM-penicillin G diluted with normal saline to a concentration of 10,000 units/ml), positive control (histamine base 1.0 mg/ml)) and negative control (normal saline). Read in 15-20 minutes:

- If change in diameter of wheal is <3 mm than that observed with the negative control, test is negative, proceed to intradermal test
- If change in diameter of wheal is ≥3 mm that that observed with the negative control, test is positive. As soon as a positive response is observed, the solution should be wiped off the skin. Patient is NOT to receive penicillin.
- The positive control (histamine skin test) should be positive to ensure the results are not falsely negative.

Step 2) Intradermal test (upper, outer arm, sufficiently below the deltoid muscle or the inner volar aspect of the forearm) conducted only if the puncture or prick test is negative. Using a 26-30 gauge, short bevel needle, withdraw the contents of the ampule and inject a sufficient amount of benzylpenicilloyl polylysine to raise a small intradermal bleb of about 3 mm in diameter; in duplicate at least 2 cm apart. Mark the margins of initial bleb with a pen. Using separate syringes and needles, inject a like amount of penicillin G [MDM-diluted to 10,000 units/ml] in duplicate at least 2 cm apart and a single intradermal test using the negative control, spaced at least 5 cm apart from the antigen test sites. Read in 20 minutes:

- If there is no increase in the original bleb and no greater reaction than the negative control site, test is negative.
- If bleb or wheal increases >2 mm from its original size or is >2 mm larger than the negative controls, the test is positive. Patient is NOT to receive penicillin
- If the negative control (saline) site exhibits a wheal >2-3 cm, repeat the test. If the same reaction is observed, a provider experienced in allergy skin testing should be consulted.

Step 3) (Optional) Oral penicillin (e.g., amoxicillin 250 mg administered in a monitored setting for 45-60 minutes) challenge if both puncture and intradermal tests are negative. However, this step is considered as optional since these tests are rarely positive after negative skin testing.

Precautions/Contraindications:

- The value of this benzylpenicilloyl polylysine as a skin-test reagent has not been established for pediatric patients or adult patients who give no history of clinical penicillin hypersensitivity.
- The ability of benzylpenicilloyl polylysine to rule out cross-reactivity to other cephalosporins/semisynthetic penicillins is not known.
- Response to skin testing may be blunted by use of interfering drugs including H1-antihistamines and vasopressors. Recommend delaying skin testing until the effect of interfering medications has dissipated.
  - 24 hours for chlorpheniramine maleate or fexofenadine
  - 4 days for diphenhydramine hydrochloride
  - 3 weeks for hydroxazine or phenathiazines
- Contraindication: Patients with a history of extreme hypersensitivity to penicillin (Toxic Epidermal Necrolysis, Stevens - Johnson syndrome, or anaphylaxis from penicillin or benzylpenicilloyl polylysine administration) or a systemic or marked local reaction to penicillin skin testing should NOT be skin tested for penicillin hypersensitivity.

Drug Interactions:

- Taking antihistamines within a 24-hour period of administering benzylpenicilloyl polylysine may interfere with skin testing. Skin test response may be attenuated in the presence of antihistamines or vasopressors (see precautions/contraindications for recommendations).

Introduction

Benzylpenicilloyl polylysine (Pre-Pen) had previously been available on the market since its original FDA approval in 1974, until 2004 when the manufacturer (HollisterStier Laboratories) had voluntarily withdrawn the product from market due to the lack of dedicated manufacturing facilities.[1] The production

of benzylpenicilloyl polylysine was abandoned, rendering the product unavailable in the marketplace since 2004. It was not until September 2009, when another manufacturer (AllerQuest, LLC) received FDA approval of benzylpenicilloyl polylysine to bring Pre-Pen back to market to be utilized in the assessment of sensitization to penicillin in patients suspected of having clinical hypersensitivity to penicillin. It is currently available as a single source product.

Penicillin allergy is one of the most common self-reported drug allergies, estimated to affect 5-10% of patients.[2] However, nearly 90% of those patients reporting an allergy to penicillin are found not to have a positive skin test and are able to tolerate penicillin type antibiotics.[3] Roughly 10% of patients who report a severe allergic reaction to penicillin will remain intolerant their entire lives, the remaining will stop expressing the penicillin specific IgE (through time) and can be safely treated with penicillin.[15]

Generally, skin testing should be considered for patients only after obtaining a detailed history of the patient's reaction to penicillin, and includes testing with both the major determinant (benzylpenicilloyl polylysine) and the minor determinant mixture (MDM), usually consisting of diluted penicillin G (diluted with normal saline to a concentration of 10,000 units/mL).[4] Diluted MDM is not available commercially. The use of benzylpenicilloyl polylysine alone would detect between 75-90% of all positive reactions. With the addition of the MDM (diluted penicillin G), detection will improve by 5-10%.[5] Penicillin skin testing should also involve use of a positive (histamine) and negative (saline) control.

For patients who report a history of penicillin allergy but have negative skin test responses to benzylpenicilloyl-polylysine and MDM, and are thus given full doses of penicillin, IgE-mediated reactions occur in 2-15% of patients. These reactions are almost always mild and self-limited. Anaphylaxis to penicillin has not been reported in skin test–negative patients in the United States. When penicillin is given after negative skin tests, about 1% to 3% of patients have urticarial or other mild cutaneous reactions. [5]

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating benzylpenicilloyl polylysine for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics

Benzylpenicilloyl polylysine is a skin test antigen reagent that reacts with the specific benzylpenicilloyl immunoglobulin E (IgE) antibodies, initiating the release of chemical mediators producing a near immediate wheal and flare reaction at the site of skin testing. All individuals exhibiting a positive skin test to benzylpenicilloyl polylysine possess IgE against the benzylpenicilloyl structural group, which is a hapten.

Benzylpenicilloyl polylysine is the major determinant of penicillin IgE mediated allergy (Type I) and is responsible for 90% of all Type I allergies. Despite this, many individuals reacting positively to benzylpenicilloyl polylysine will not develop a systemic allergic reaction on subsequent exposure to therapeutic penicillin, especially those who have not reacted to penicillins previously. Thus, the benzylpenicilloyl polylysine skin test determines the presence of penicilloyl IgE antibodies, which are necessary for the positive reaction to occur, but not quite sufficient for development of acute allergic reactions from the major penicilloyl determinant.[4]

Typically, IgE-mediated (immediate-type) reactions include pruritis, urticaria, angioedema, wheezing, bronchospasm and anaphylaxis. These reactions can occur within minutes after drug administration but certain factors may delay the allergic reaction for up to an hour (e.g., oral administration, delayed absorption from food, etc.).[6,7]

Non-benzylpenicilloyl haptens are considered as minor determinants because they less frequently elicit an immune response in penicillin-treated individuals. However, they can be associated with significant hypersensitivity. Minor determinants include penicillin G, penicilloate, and penilloate, representing about 8-9% of all Type I allergies.[8] A reagent containing the minor determinants is not available commercially in

the United States but skin testing with diluted penicillin G accomplishes testing for these minor determinants. [4,8-9]

FDA Approved Indication(s)

For the assessment of sensitization to penicillin (benzylpenicillin or penicillin G) in patients suspected to have clinical penicillin hypersensitivity.

Potential Off-label Uses

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

Off-label uses may include:
1) Use of benzylpenicilloyl polylysine in patients with no prior exposure to penicillin, or prior history of allergy or hypersensitivity to penicillin to predict whether an allergic reaction may occur. At this time, there is no evidence to support use in patients with no prior exposure to penicillin or no prior history of penicillin hypersensitivity.
2) Use of benzylpenicilloyl polylysine to rule out cross-reactivity to other cephalosporins/semisynthetic penicillins in patients with or without a prior history of hypersensitivity to penicillin, cephalosporins or semisynthetic penicillins. At this time, there is limited evidence to support use of this antigen reagent to determine cross-reactivity in patients with or without a prior history of sensitivity to penicillin, cephalosporins or semisynthetic penicillins.

Current VA National Formulary Alternatives

None available.

Dosage and Administration [7, 17-20]

The skin test antigen should always be applied first by the puncture/prick technique (step 1) followed by the intradermal test (step 2) only if a negative test result is obtained. All skin testing should be performed on the inner volar aspect of the forearm.

Because of the risk of potential systemic allergic reactions (IgE-mediated reactions to penicillin), skin testing should be performed in an appropriate health care setting under direct medical supervision.

In their prescribing information, the manufacturer details the necessary steps involved in properly utilizing benzylpenicilloyl polylysine, as follows:

Step 1: Puncture technique (Must be performed prior to the intradermal test):
After preparing the skin surface, apply a small drop of benzylpenicilloyl-polylysine solution using a sterile 22- to 28-gauge needle; the same needle can then be used to make a single shallow puncture of the epidermis through the drop of solution. Very little pressure is required to break the epidermal continuity. Observe for the appearance of a wheal or erythema, and the occurrence of itching at the test site during the succeeding 15 minutes, at which time the benzylpenicilloyl-polylysine solution over the puncture site should be wiped off. A similar procedure should be followed for skin testing with the MDM (diluted penicillin G) and positive (histamine) and negative (saline) controls. A positive reaction consists of the development within 10 minutes of a pale wheal, sometimes with pseudopods, surrounding the puncture site and varying in diameter from 5 to 15 mm (or more). This wheal may be surrounded by a variable diameter of erythema, and accompanied by a variable degree of itching. The most sensitive individuals develop itching quickly, and the wheal and erythema are prompt in their appearance. As soon as a positive response as previously defined is clearly evident, the solution over the scratch should be immediately wiped off. If the puncture test is either negative (wheal <3mm) or equivocally positive (less than 5 mm wheal with little or no erythema and no itching), an intradermal test may be performed.

Step 2: Intradermal test:
Using a 26-30 gauge, short beveled needle, withdraw the contents of the benzylpenicilloyl polylysine from the ampule. Insert the needle bevel up immediately below the skin surface; inject enough benzylpenicilloyl polylysine solution to create a small intradermal bleb of about 3 mm in diameter. Most skin reactions will develop within 5 to 15 minutes and response to the skin test is read at 20 minutes as follows: negative response is no increase in size of original bleb and no greater reaction than the control site; ambiguous response is wheal only slightly larger than initial injection bleb, with or without accompanying erythematous flare and slightly larger than the control site, or discordance between duplicates; positive response is itching, significant increase in size of original blebs to at least 5 mm, and wheal may exceed 20 mm in diameter and exhibit pseudopods. If the control site exhibits a wheal more than 2 to 3 mm, repeat the test; if the same reaction is observed, a health care provider experienced with allergy skin testing should be consulted.

It is recommended that intradermal skin testing for penicillin allergy is conducted using both benzylpenicilloyl polylysine (Pre-Pen®, major determinant) and penicillin G(minor determinant) diluted to 10,000 units/mL with normal saline along with a negative (normal saline) control. The intradermal skin testing procedure for MDM and negative control are similar to that performed with benzylpenicilloyl polylysine as listed above, however, the negative control test site should be spaced apart by at least 5 cm from the antigen test sites, [8-9,20] The use of an oral penicillin challenge (after observing negative skin tests) is optional since such tests are rarely positive after negative skin test results are observed.

Benzypenicilloyl polylysine 0.25mL ampules should be kept refrigerated, 2° to 8°C (36° to 46°F). Discard any unused portion. Solutions subjected to ambient temperatures for more than 24 hours should be discarded.

Efficacy

Efficacy Measures

The entirety of efficacy measures assessing benzylpenicilloyl polylysine help determine the predictive power of the penicillin skin test. The main efficacy measures utilized throughout the clinical trials include examining patients who have had previous penicillin treatment (with and without reported history of allergic reactions) and compare them to the outcome of the benzylpenicilloyl polylysine skin test. One outcome measure assessed the occurrence and type of systemic reactions, if any, with benzylpenicilloyl polylysine. The type of reaction and the time to onset of that reaction are important markers to determine future use of penicillin treatment. This would help ensure the validity of the skin test and usefulness of the test in larger patient populations.

A negative skin test to benzylpenicilloyl polylysine is associated with an incidence of immediate allergic reactions of less than 5% after the administration of therapeutic penicillin, whereas the incidence may be more than 50% in a history-positive patient with a positive skin test to benzylpenicilloyl polylysine.[6] In general, these reactions are mostly dermatologic in nature. There is insufficient evidence to determine the relative risk between patients with a history of penicillin hypersensitivity compared to those with a positive skin test to benzylpencilloyl polylysine, when determining the risk of penicillin treatment in individual patients. To date, it has not been established whether a negative skin test to benzylpenicilloyl polylysine predicts a lower risk of anaphylaxis.

The formulation of this reagent is unchanged from the original product first introduced in the 1970's. Therefore, no new trials were required by the current manufacturer in order to re-seek FDA approval as a single source product. Most trials were published at the time of original approval.

Summary of Efficacy Findings
A total of four studies were considered for this review. Three were included in the product's original FDA approval and were obtained from the manufacturer of benzylpenicilloyl polylysine. The fourth, more recent study was included to demonstrate the safety and efficacy of benzylpenicilloyl polylysine in helping to determine whether use of beta-lactam antibiotics is possible in those patients with a prior history of an immediate hypersensitivity reaction to these antibiotics. The included studies were not randomized and statistical analyses, other than a p-value, were not performed; with many authors simply reporting raw data.

One of the studies compared penicilloyl-polylysine with penicillin G to determine which agent would better detect allergy to penicillin. Investigators studied 1,153 patients, each were tested with the two agents. The overall positivity rate for patients who were tested with penicilloyl-polylysine was 9.2% compared with 6.2% with penicillin G. The difference was statistically significant. [10]

In another study, 1,022 naval recruits, participating in a mass penicillin prophylaxis program to combat a high incidence of streptococcal infections, all received benzathine penicillin as part of their routine military vaccinations. Soldiers were interviewed regarding past penicillin use, penicillin allergy and personal and family history of atopy. Intradermal penicilloyl polylysine was administered to determine its usefulness as a penicillin skin test reagent. No comparator was used, penicilloyl polylysine was the only agent tested. he authors described that patients with a prior history of penicillin allergy had a significantly higher incidence of positive skin reactions (35%) than did non-allergic individuals (6.8%). It was reported that only 3% of individuals who had never received penicillin treatment had positive skin reactions compared to 8.4% of those who had received penicillin, indicating the importance of the previous exposure. For patients who had no self-reported history of penicillin allergy (n=825), three patients who were skin-test positive developed reactions (5.2%), two of which were considered strongly positive and one was considered weakly positive. Seven patients of the skin-test negative subjects (with no reported history of penicillin allergy) developed a reaction (0.9%). No subjects developed anaphylaxis.[11]

A third study prospectively examined 5,461 patients presenting to a large urban venereal disease clinic. Patients were separated into three groups based upon their prior exposure and allergy to penicillin, as follows: 1) previous penicillin therapy, no allergy; 2) previous penicillin therapy, definite or probable allergy; 3) no previous penicillin. Patients were given an intradermal test of penicilloyl polylysine to determine whether they exhibited a positive skin test and whether or not they could be re-challenged with penicillin. No comparator was used, penicilloyl polylysine was the only agent tested. Of the 124 patients reporting a history of penicillin allergy, only 41 had a positive reaction and 83 reported a negative reaction. Of those with a positive reaction, five patients whose reactions weren't considered strongly positive were re-challenged with penicillin therapy. None of these patients developed an allergic reaction to penicillin treatment. Of the 83 patients who reported a negative reaction, 36 were re-challanged with penicillin treatment. One patient developed urticaria and pruritis within 48 hours of penicillin treatment.[12]

In a more recently published study, investigators performed skin-testing using benzylpenicilloyl polylysine and a minor determinant mixture in 80 patients with a history of hypersensitivity to beta lactam antibiotics. If the skin test was negative (n=59 patients), the patient was then re-challenged with a skin test of the offending drug. This second test (offending drug) was positive for three patients, with two patients displaying hypersensitivities to cefuroxime and one patient being hypersensitive to cefixime. Of the remaining patients who did not react to a re-challenge with the offending drug (n=53 patients), 40 elected to take a drug provocation test. This was done in a double blind, placebo controlled fashion challenging the patient with up titrated doses of amoxicillin and placebo on separate days for a 24-hour period. If the provocation test resulted in a negative response or reaction, the patient was recommended to use beta lactam antibiotics in the future whenever their use was indicated. In the 40 patients who underwent drug provocation testing, 35 patients exhibited a negative response, showing no hypersensitivity to beta lactams; 4 patients exhibited a positive test to amoxicillin and 1 patient had a positive reaction to ampicillin. Of the patients tested, 9 patients were observed to exhibit a positive response to the benzylpenicillin polylysine skin test, and 12 patients had a positive response to the minor determinant mixture. The results did not include any statistical significance of values provided.[13] The authors concluded that although the recently reintroduced penicillin tests provide sufficient allergy data, all steps recommended by the European Network for Drug Allergy (ENDA) be followed when determining the possibility of immediate reactions to beta-lactams (Figure 1-located in appendix)[14].

For further details on the efficacy results of the clinical trials, refer to the Appendix (page 10).

Adverse Events (Safety Data)

Some patients may develop an intense local inflammatory response at the skin test site. In rare cases, patients may develop systemic allergic reactions from skin testing with benzylpenicilloyl polylysine. These

reactions may manifest as generalized erythema, pruritis, angioedema, shortness of breath, hypotension and anaphylaxis.

When treating a benzylpenicilloyl polylysine induced reaction, it is recommended that a venous occlusion tourniquet be applied proximal to the skin test site and epinephrine be administered. The patient should be kept under observation for several hours.

Deaths and Other Serious Adverse Events

No deaths were reported after the use of benzypenicilloyl polylysine.

Anaphylaxis: There is small risk of anaphylaxis from the skin test reagent itself. This risk is unknown but believed to be rare.[7] There is one study from a sexually transmitted disease (STD) clinic involving 5,063 patients who were skin-tested using benzylpenicilloyl polylysine and the minor determinant mixture. An anaphylactic reaction occurred in one patient. In this case, systemic urticaria developed immediately after the intradermal skin test and the patient complained of generalized pruritus, nausea, and dizziness. Mild hypotension was observed and wheezing was heard on auscultation. The patient was treated with epinephrine and diphenhydramine hydrochloride and responded immediately. This patient had had an urticarial reaction to penicillin 17 years previously. The authors attributed the reaction to the minor determinant mixture and not the benzylpenicilloyl polylysine. The wheal size during the treatment of this acute reaction was not measured.[9]

In the same study, urticarial reactions occurred in three patients after skin testing with benzylpenicilloyl polylysine. One was generalized, another was localized to the shoulders, face, and neck, and in the third, urticarial lesions were limited to the forearm that was skin-tested. Six subjects experienced generalized pruritus without any skin lesions, while pruritus of the periorbital area occurred in one. All reactions occurred 5 to 25 minutes after skin testing. Diphenhydramine was administered intramuscularly to four patients and oral diphenhydramine was given to five patients. All reactions subsided promptly after treatment of the adverse reaction.[9]

Contraindications

Absolute contraindications:

- Patients known to be extremely hypersensitive (including but not limited to Toxic Epidermal Necrolysis, Stevens - Johnson syndrome, or anaphylaxis) to penicillin should not be skin tested.
- Patients who have experienced a systemic or marked local reaction to prior administration of the benzylpenicilloyl polylysine skin test should not be skin tested.

Warnings and Precautions[7]

Warnings:

The risk of sensitization to repeated skin testing with benzylpenicilloyl polylysine is unknown. There is a possibility of a systemic allergic reaction occurring following a skin test, including anaphylaxis. To minimize the risk of this occurring, a puncture skin test should be performed first. Intradermal skin testing should be performed only if the puncture test is entirely negative.

Precautions:

General: No reagent, test, or combination of tests will completely assure that a reaction to penicillin therapy will not occur.

The value of benzylpenicilloyl polylysine skin test alone as an indicator of assessing the risk of administering therapeutic penicillin (when penicillin is the preferred drug of choice) has not been established for the following situations:

1) Adult patients who give no history of clinical penicillin hypersensitivity
2) Pediatric patient populations

The clinical value of benzylpenicilloyl polylysine is unknown in the following circumstances:

- When exposure to penicillin is suspected as a cause of a current drug reaction.
- In patients who are undergoing routine allergy evaluation or testing.
- In determining the risk of administering semisynthetic penicillins (phenoxymethyl penicillin, ampicillin, carbenicillin, dicloxacillin, methicillin, nafcillin, oxacillin, amoxicillin), cephalosporin-derived antibiotics, and penem antibiotics.

In addition to the results of the benzylpenicilloyl polylysine skin test, individual patient factors must be considered when deciding whether to administer penicillin. The manufacturer recommends keeping the following in mind when making penicillin treatment decision:

- A serious allergic reaction to therapeutic penicillin may occur in a patient with a negative skin test to benzylpenicilloyl polylysine.
- It is possible for a patient to have an anaphylactic reaction to therapeutic penicillin in the presence of a negative benzylpenicilloyl polylysine skin test and a negative history of clinical penicillin hypersensitivity.
- If penicillin is the drug of choice for a life-threatening infection, successful desensitization with therapeutic penicillin may be possible irrespective of a positive skin test and/or a positive history of clinical penicillin hypersensitivity.

Pregnancy: Category C
Animal reproduction studies have not been conducted with benzylpenicilloyl polylysine. It is not known whether benzylpenicilloyl polylysine can cause fetal harm or affect a woman's ability to reproduce. The risks of skin testing in these patients should be weighed against the risk of penicillin therapy without skin testing.

Postmarketing Safety Experience (Optional)

No data

Sentinel Events

No data

Look-alike / Sound-alike (LA / SA) Error Risk Potential

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:
LA/SA for generic name <*benzylpenicilloyl polylysine*>: <*Benzoyl Peroxide, Penicillamine, Penicillin G inj, PPD*>
LA/SA for trade name <*Pre-Pen*>: <*Epi-Pen*>

Drug Interactions

Drug-Drug Interactions

Providers should be aware that skin-testing responses may be blunted by interfering drugs (eg, H_1 antihistamines, vasopressors). As a result, skin testing should be delayed until the effects of such drugs have dissipated, or a separate skin test with histamine can be used to evaluate persistent antihistaminic effects in vivo.
The following medications should not be used prior to using benzylpenicilloyl polylysine[15]

- Within 24 hours,of use of chlorpheniramine maleate, fexofenadine
- Within 4 days of use of diphenhydramine hydrochloride
- During the preceding 3 weeks of use of hydroxyzine or phenathiazines

Comparative Cost

Please refer to the last page of this document for VA acquisition costs for benzylpenicilloyl polylysine. Prices shown on the last page of this internal, draft document may include additional discounts available to VA. This information is considered strictly confidential and must not be shared outside of VA. All cost information will be removed from the document when posted to the PBM website.

Pharmacoeconomic Analysis

None available

Conclusions

Hypersensitivity to penicillin treatment is relatively rare; however, the number of patients who report an allergy to penicillin is more common. Benzylpenicilloyl polylysine (Pre-Pen®) is a skin-test reagent which has been reintroduced to the market as a diagnostic tool to aid providers in determining if a patient, based on previous experience of developing a reaction to penicillin, will be able to utilize penicillin antibiotic therapy. The use of skin testing with benzylpenicilloyl polylysine along with penicillin G can identify up to 97% of all positive reactions to penicillin. In those patients with a negative skin test, less than 5% will have an immediate allergic reaction compared to more than 50% of patients having a positive skin test after use of therapeutic penicillin. It is not known whether a negative skin test predicts a lower risk for anaphylaxis. No reagent, test, or combination of tests will completely assure that a reaction to penicillin therapy will not occur.

Evidence for PCN skin testing in more than 20,000 patients with a reported hypersensitivity to penicillin has shown that these persons can be re-treated safely with penicillin or related antibiotics if intradermal skin tests with benzylpenicilloyl polylysine and a suitable MDM are negative.[9,16]

There is a risk of developing systemic allergic reactions, including anaphylaxis, upon skin testing with benzylpenicilloyl polylysine. Skin testing with benzylpenicilloyl polylysine (along with penicillin G) involves a two-step process in which puncture /prick testing is performed prior to intradermal testing to reduce the risk of systemic reactions. Intradermal testing is only performed if the puncture test is entirely negative. Penicillin skin testing also involves use of a positive (histamine) and negative (saline) control. Because of the risk for systemic allergic reactions, skin testing should be performed in an appropriate healthcare setting with direct medical supervision.

The value of benzylpenicilloyl polylysine as a skin test reagent has not been established for pediatric patients or adult patients with no prior history of clinical hypersensitivity to penicillin. In addition, the clinical value of skin testing is unknown in determining the risk of administering semisynthetic penicillins (phenoxymethyl penicillin, ampicillin, carbenicillin, dicloxacillin, methicillin, nafcillin, oxacillin, amoxicillin), cephalosporin-derived antibiotics and penen antibiotics.

The availability of benzylpenicilloyl polylysine allows patients, who may have previously believed that treatment with penicillin was not an option, to undergo skin testing to determine if treatment with therapeutic penicillin is an acceptable choice. In addition, the availability of Pre-Pen may lead to reduced use of broad spectrum antibiotics in those patients reporting a prior history of an allergy to penicillin.

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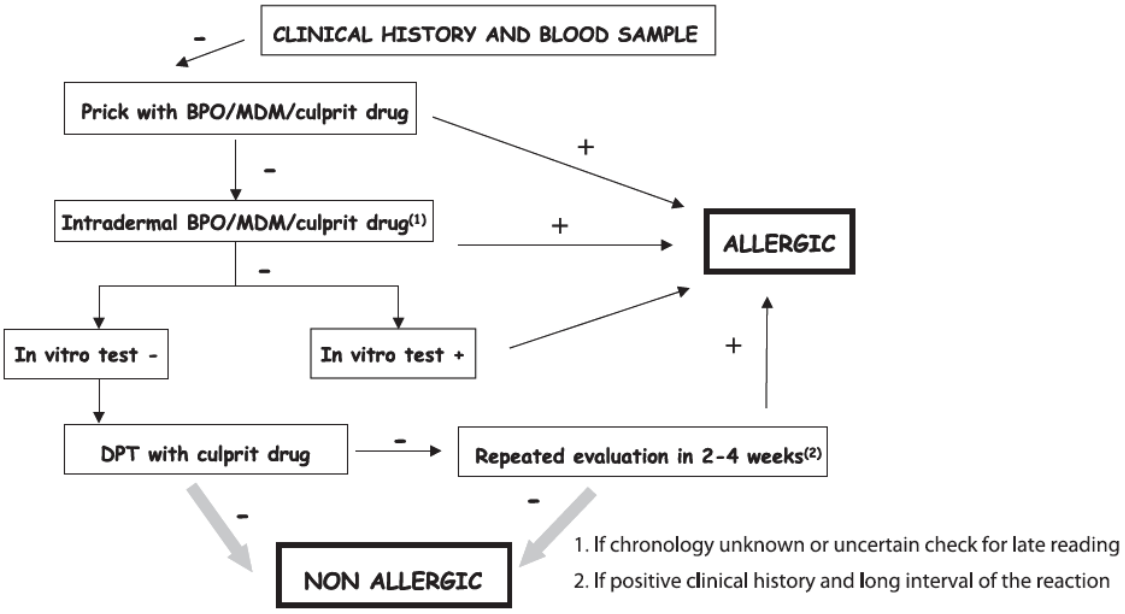
19. Interpretation of skin testing (Pre-Pen) Alk-Abello. http://www.pre-pen.com/files/PREPEN_Skin_Testing_Guideline.pdf
20. Procedure for Penicillin Skin Testing/Required Supplies for Penicillin Skin Testing. Alk-Abello. Handout provided by manufacturer.

Prepared 5/12 Contact person: Rushabh Shah, PGY-1 Managed Care Pharmacy Resident, and Cathy Kelley, Pharm.D. cathy.kelley@va.gov

Appendix:

Figure 1. (ENDA Diagnostic Algorithm) [14]



<table>
<tr><td>Citation</td><td>Green GR and Rosenblum, A. Report of the Penicillin Study Group-American Academy of Allergy. Journal of Allergy and Clinical Immunology 1971 Dec;48 (6): 331-343.</td></tr>
<tr><td>Study Goals</td><td>Investigate the correlation of the history of penicillin allergy and results from penicillin skin testing.</td></tr>
<tr><td>Methods</td><td>Study Design
Patients who were included in the study were interviewed and a comprehensive clinical history was taken with particular attention to previous penicillin therapy and reaction. There was a standardized questionnaire used and response form utilized. Interviews were taken by 26 different clinical investigators across multiple sites nationally. Two preparations were used for skin testing: 1) penicilloyl-polylysine (PPL) and 2) benzylpenicillin (penicillin G). After initial scratch testing technique was completed and showed a negative result, intradermal skin test were then performed.
A standardized technique was recommended for the intradermal skin tests: creation of an initial bleb with the testing reagents. The reactions were recorded in the same manner:
1) Time required for the appearance of a reaction
2) The size of the erythema, if any
3) The size of the wheal, if any

Responses to skin tests were positive, negative, or ambiguous. Ambiguous skin reactions were considered “erythema only.”

The patients in this study were not randomized to any particular group. The length of study duration was not indicated.

Data Analysis
The power of this study was not conducted; only the statistical significance was calculated and presented (P-value).</td></tr>
<tr><td>Criteria</td><td>Inclusion criteria
Patients were included if they subjected to allergy investigation as well as selected patients being evaluated for a history of penicillin hypersensitivity were interviewed and skin tested for penicillin hypersensitivity.
Exclusion criteria
There was no information given regarding any exclusion criteria.</td></tr>
<tr><td>Results</td><td>A total of 1,153 cases were reviewed. The results are in the following tables:

The overall positivity rate was higher for PPL (9.8%) than for PG (6.2%). This was found to be
<table>
<tr><td colspan="5">Table I</td></tr>
<tr><td colspan="5">A: Distribution of skin reactions to penicilloyl-polylysine (PPL) and penicillin G (PG)</td></tr>
<tr><td>Reagents:</td><td>PPL (+)/ PG (-)</td><td>PPL (+)/ PG (+)</td><td>PPL (-)/ PG (+)</td><td>PPL (-)/ PG (-)</td></tr>
<tr><td>No. of Patients: (%)</td><td>79 (6.9%)</td><td>34 (3.0%)</td><td>38 (3.3%)</td><td>1002 (86.9%)</td></tr>
<tr><td colspan="6">B: Totals</td></tr>
<tr><td></td><td>PPL (+)</td><td>PG (+)</td><td>Total (+)</td><td>Total (-)</td><td>Total Tested</td></tr>
<tr><td>No. of Patients (%)</td><td>113 (9.8%)</td><td>72 (6.2%)</td><td>151 (13.1%)*</td><td>1002 (86.9%)</td><td>1,153 (100%)</td></tr>
</table>
* includes patients who were positive to both PPL and PG(34 patients)
statistically significant (P<0.003). A greater number of patients reacted only to PPL (79) than to
<table>
<tr><td colspan="4">Table II</td></tr>
<tr><td colspan="4">Distributions of skin reactions to PPL and PG, by treatment group</td></tr>
<tr><td></td><td>PPL (+)</td><td>PG (+)</td><td></td></tr>
<tr><td>Group</td><td>No. of occurrences (%)</td><td>No. of occurrences (%)</td><td>P-Value</td></tr>
<tr><td>Group I: Prev. penicillin treatment, no history of penicillin allergy (675 patients)</td><td>36 (5.3%)</td><td>24 (3.6%)</td><td>P <0.20</td></tr>
<tr><td>Group II: Prev. penicilin treatment, history of penicillin allergy (352 patients)</td><td>73 (20.7%)</td><td>47 (13.3%)</td><td>P <0.02</td></tr>
<tr><td>Totals (1,027 patients)</td><td>109 (10.6%)</td><td>71 (6.9%)</td><td>n/a</td></tr>
</table>
PG (38), this was also found to be statistically significant (P<0.001).</td></tr>
</table>

Patients who have had previous hypersensitivity to penicillin (Group II) show a significantly higher positivity rate for both reagents than those who have had no such reactions following therapy, (P<0.001, for both reagents).

Table III

Distribution of positive skin tests in penicillin allergy patients with a history of penicillin hypersensitivity

Time of penicillin reaction after therapy	Total PPL (+) No. of occurrences (%)	Total PG (+) No. of occurrences (%)	P-Value
Within 30 minutes (31 patients)	26 (83.9%)	17 (54.8%)	P <0.03
Between 30 minutes and 24 hours (26 patients)	21 (80.8%)	17 (65.4%)	n/a
More than 24 hours (33 patients)	24 (72.7%)	17 (51.5%)	P <0.20

Table IV

Distribution of positive skin tests responses by type of hypersensitive reaction

Type of hypersensitivity reaction	Total PPL (+) No. of occurrences (%)	Total PG (+) No. of occurrences (%)	P-Value
Skin reaction only (309 patients)	66 (21.4%)	39 (12.6%)	P <0.006
Visceral (with or without skin reaction-43 patients)	10 (23.3%)	14 (32.6%)	P<0.02
No reactions (675)	36 (5.3%)	24 (3.6%)	n/a

Table V

Distribution of positive skin tests responses by history of penicillin therapy

History of therapy	Total PPL (+) No. of occurrences (%)	Total PG (+) No. of occurrences (%)	P-Value
One dose (152 patients)	24 (15.8%)	17 (11.2%)	P <0.001
One course (249 patients)	14 (5.6%)	8 (3.2%)	P<0.03
Multiple doses (177 patients)	14 (7.9%)	10 (5.6%)	n/a

Table VI

Intensity of skin reactions versus history of penicillin allergy

History of	Reagent	Skin reactions

	penicillin allergy		Weak (< 8mm)	Strong (> 8mm)
	No	PPL	20/148 (14 %)	13/148 (9%)
		PG	8/140 (6%)	8/140 (6%)
	Yes	PPL	31/153 (20%)	27/153 (18%)
		PG	22/134 (16%)	7/134 (5%)

The potential that a patient's age could play a confounding variable was considered. This was especially true as there were a large number of patients who reported history of penicillin intolerance but had negative skin tests. As this was further looked into, patients with a history of penicillin allergy, 72% of those who were 15 years old or less had negative skin tests, this is in contrast to 62% of those who were greater 15 years old having negative skin reactions.

Conclusions	The results of this study show a correlation between skin-testing with history of clinical penicillin hypersensitivity. However, there were not enough patients challenged with penicillin treatment to determine if clinical history or skin-testing is more predictive of penicillin hypersensitivity. The authors suggest that patients who have reacted to the two skin-test reagents are likely to develop an immediate hypersensitivity to penicillin. Both reagents should be used for testing purposes to detect (with high likelihood) if a patient will immediately become sensitive to penicillin. Skin testing with the reagents penicilloyl-polylysine and benzylpenicillinG was shown to be safe and of value in this study and should be performed prior to administering therapeutic penicillin. The authors believe that these skin testing reagents can be used safely by a large number of practicing physicians to show the true value of this procedure.
Critique	**Strengths** This study showed that overall; hypersensitivity with penicillin is relatively rare. This study adds to the data that penicillin skin testing is safe and can be a valuable tool in determining penicillin hypersensitivity. **Limitations** It was unclear if all patients had received both intradermal skin tests; unclear if all patients had received both skin tests in the same arm and at the same time. There are many points in this study where potential for error may unravel: there were a large number of investigators, which may have led to a deviation from the standardized protocol. There was a large dependence on the accuracy of previous medical records and histories given by patients (including previous penicillin allergy). These could lead to many inaccuracies. Interpretation of skin tests may be another inherent problem with this study. The determination of a skin reaction is subjective to the interpreter; as there were have been many ambiguities present throughout the study. As the patient characteristics were not provided in the study, the validity of this patient population to the VA population is unknown. It cannot be said for certain the VA population will parallel the results of this study.

Citation	**Rytel MW, Klion FM, Arlander TR and Miller LF. Detection of penicillin hypersensitivity with penicilloyl-polylysine. Journal of the American Medical Association 1963 Dec;186 (10): 894-898.**
Study Goals	To determine the correlation between skin reactions and systemic penicillin allergy using penicilloyl-polylysine administered as a skin test.
Methods	**Study Design** The treatment group consisted of 1,022 naval recruits (955 Caucasian and 67 African Americans) who were to be given 1.2 million units of benzathine penicillin G intragluteally as part of routine military-training vaccination schedule. This was to be done as a part of a mass penicillin prophylaxis program to combat a high incidence of streptococcal infections with risk of rheumatic fever in military populations. Each recruit was interviewed by a medical officer who collected a history of the patient's penicillin allergy, previous penicillin treatment, and personal and familial atopic history. Post intradermal injection of penicilloyl-polylysine (on patient's forearm) the area and size of the skin where injected (bleb) was marked and reassessed twenty minutes later to indicate any development of a wheal and erythema. The reactions were classified based on increase in size of original bleb and size of any wheal formation. The reactions were classified as: 1) Negative- no increase in size of original bleb; wheal less than 8mm in diameter 2) Weakly Positive- definite increase in size of original bleb; wheal 8-12mm in diameter 3) Strongly Positive- Marked increase in size of original bleb; wheal over 12mm in diameter This study was not randomized. The entire length of the study took place over a period of nine weeks (over the course of one naval recruitment camp). Efficacy measures include: 1) Relationship between previous penicillin treatment and penicilloyl-polylysine skin test results 2) Relationship between history of penicillin allergy and penicilloyl-polylysine skin test results, 3) Relationship of systemic reactions following penicillin to penicilloyl-polylysine skin test results **Data Analysis** There was no information provided on power analysis and statistical tests utilized in the trial. Statistical significance was all that was calculated.
Criteria	**Inclusion criteria** All naval recruits, regardless of the skin reaction unless they fell into exclusion criteria below. **Exclusion criteria** Individuals identified by history as allergic to penicillin (with clear histories for anaphylaxis) were excluded from benzathine penicillin G administration.
Results	Of the 1,022 individuals studied, 868 had previous penicillin treatment, 125 had no previous penicillin treatment and 29 were unknown. Of the previous penicillin treatment group, 8.4% (73/868) showed a positive skin test. This was compared to 3% (4/125) who showed a positive skin test in the no previous penicillin treatment arm. This difference was found to be statistically significant ($P<0.05$). Of the 868 individuals whom previously trialed penicillin, 43 reported a previous allergic episode following penicillin administration and 825 had a negative history of penicillin allergy. The total incidence of positive skin reactions was 35% (15/43) in the penicillin-allergic and 6.8% (58/825) in the non-allergic subjects. These differences were found to be statistically significant ($P <0.001$). Of the individuals with a negative history of penicillin allergy, who were treated with penicillin (n=825), the rate of systemic reactions following treatment was assessed. Three reactions occurred in skin-test positive subjects (incidence= 5.2%), two of whom were considered strongly positive and one was considered weakly positive. Seven reactions occurred in skin-test negative subjects (incidence=0.9%). This difference in incidence between positive and negative subjects is statistically significant ($P<0.05$). Of the seven individuals with reactions who were originally skin-test negative, were re skin-tested two to three weeks following their reactions. Only one individual had converted to a positive skin-test. No patient experienced any anaphylaxis.
Conclusions	The authors described that naval recruit subjects with histories of penicillin allergy had a significantly higher incidence of positive skin reactions (35%) than did non-allergic individuals (6.8%). It was shown that only 3% of individuals who had never been under penicillin treatment had positive skin reactions compared to 8.4% of those who had; indicating the importance of the previous exposure. They also noted that there appears to be a decrease in the incidence of system skin reactions with an increase in the time interval between the last dose of penicillin and the occurrence of the penicillin reaction. The test material is believed to hold promise, but further observations will undoubtedly be required to define some of the variables involved and perhaps to increase its sensitivity.
Critique	**Strengths:** Include the patient population observed (naval recruits), although younger during the timeframe in which this study took place, a majority of these patients are likely to join the VA healthcare system after their tour of duties in the navy. This patient population is very generalizable to the VA patient population. **Limitations:** There was a lack of diversity among the patient population. The time onset of allergy following penicillin administration was asked as part of the interview by the medical officer. This

	outcome was looked into any further.
Citation	**Lentz JW and Nicholas L. Penicilloyl-polylysine intradermal testing for penicillin hypersensitivity. British Journal of Venereal Diseases 1970; 46: 457-460**
Study Goals	To assess the use of penicilloyl-polylysine in a large patient population.
Methods	**Study Design** This study presented a prospective look at using penicilloyl-polylysine (PPL) in a large venereal disease clinic population. The adverse event rate to treatment penicillin was already known prior to study initiation. The patients varied in age from 17-87 years and they were primarily of one ethnic group. In this study, in order to keep consistency, only two physicians administered the penicilloyl-polylysine intradermal test, read and recorded the results. Skin tests were evaluated according to these categories: Negative: No increase in size of the initial bleb Positive: definite increase in the size of the original bleb Ambiguous: very slight indefinite increase in size of the original bleb Patients were divided into three treatment groups: Group I: previous penicillin therapy with no penicillin hypersensitivity Group II: previous penicillin therapy and definite/probable history of sensitivity or allergic reaction Group III: no previous penicillin therapy Patients in all three treatment groups were re-challenged with penicillin treatment if deemed appropriate by the clinic physicians. Patients whose skin responses to PPL were considered strongly positive were not re-challenged. This study did not randomize patients into treatment groups and there was no length of study indicated. **Data Analysis** There was no information provided on power analysis and statistical tests utilized in the trial.
Criteria	**Inclusion criteria** Information was not provided. **Exclusion criteria** Certain criteria included: no clinical indication for treatment; a positive penicilloyl polylysine skin test; a strong history of penicillin hypersensitivity; or any combination of the above.
Results	

Group:	**I**					
Skin Reactivity to PPL:			**-**	**+/-**	**+**	**Total**
No. of Patients	Tested		4,283	36	358	4,677
	Challenged	No. (%)	4,102 (95.7)	34 (94.5)	105 (29.3)	4,241 (90.7)
	Reacted	No. (%)	5 (0.12)	-	0	5 (0.11)

Group:	**II**					
Skin Reactivity to PPL:			**-**	**+/-**	**+**	**Total**
No. of Patients	Tested		83	-	41	124
	Challenged	No. (%)	36 (43.4)	-	5 (12.2)	41 (33.0)
	Reacted	No. (%)	1 (2.8)	-	-	1

Group:	**III**					
Skin Reactivity to PPL:			-	+/-	+	Total
No. of Patients	Tested		637	1	22	660
	Challenged	No. (%)	611 (95.9)	1 (100)	5 (22.7)	617

	<table><tr><td></td><td>Reacted</td><td>No. (%)</td><td>-</td><td>-</td><td>-</td><td>-</td></tr></table> One patient in Group II (previous penicillin treatment with positive history of penicillin hypersensitivity) developed an allergic reaction showing signs of urticaria and pruritus, developing within 48 hours. In this same group, there were five patients who were challenged with penicillin and did not have any allergic reactions. The five patients who reacted in Group I (previous penicillin treatment with negative history of penicillin hypersensitivity), developed manageable reactions: local erythema, edema at test site, and pruritus. All reacted in less than one hour, except for one person who had a delayed reaction, 48 hours. There were no occurrences of an anaphylaxis type reaction for any patients throughout the study.
Conclusions	Overall, there were 5,461 intradermal tests for penicillin hypersensitivity given. For this particular clinic, the implementation of the PPL intradermal testing program had decreased the rate of adverse reactions from 3.5% at the beginning to 0.1% near the study's completion. The authors claim that prospective skin testing with PPL appears to be safe and useful in clinical work.
Critique	**Strengths:** This study showed that penicilloyl-polylysine can be used effectively in a large patient population. The results of this study compares with other studies which were published at the time. The incidence of a skin/systemic reaction to penicillin is relatively rare. **Limitations:** There were many limitations apparent throughout the study. The patient population was not well defined. The characteristics given about the patient population were very minimal. Therefore, the results presented in this study may not be applicable to the VA patient population. There was no clear definition as to what constituted an allergic reaction vs. systemic reaction. The type of penicillin treatment used was also not given throughout the study. Likely, this was penicillin G, but it was not well defined in the study. Many comparisons made to previous studies used different formulations of penicilloyl-polylysine.