



MOC-CME Review

Penicillin desensitization: Treatment of syphilis in pregnancy in penicillin-allergic patients



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Overall Purpose

Participants will be able to demonstrate increased knowledge of the clinical treatment of allergy/asthma/immunology and how new information can be applied to their own practices.

Learning Objectives

At the conclusion of this activity, participants should be able to:

- Discuss methods for evaluating penicillin allergy and for performing penicillin desensitization procedures
- Recognize indications for penicillin desensitization
- Describe special considerations for penicillin desensitization in pregnancy

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Target Audience

Physicians involved in providing patient care in the field of allergy/asthma/immunology

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Clinical Vignette

A 44-year-old gravida 3 para 2 patient with penicillin allergy presented to her obstetrics physician with symptoms and test results concerning for syphilis infection. The allergy and immunology service was consulted for guidance, because treatment with penicillin was deemed necessary. The patient was 27 weeks pregnant and was found at routine prenatal screening to have a positive rapid plasma reagin titer of 1:128 and a positive *Treponema palladium* immunoglobulin (Ig) G test result. She had blurry vision that began in the first trimester; she also described having had a genital and palmar rash 8 months previously. The pregnancy was conceived by in vitro fertilization; she denied any sexual activity in the past 18 months. Her husband was known to have syphilis in the past, which was reportedly treated 2 years previously. She reported having a positive rapid plasma reagin reaction when tested in China during her first trimester but denied receiving any treatment herself for syphilis.

The infectious disease service team suspected that her described past genital lesions were condylomata lata, reflective of a secondary syphilis infection. On examination by ophthalmology, the patient was found to have asymmetric cupping in both eyes and temporal pallor in the left eye that was concerning to the team for possible neurosyphilis. Given concurrent pregnancy and syphilis infection, the infectious disease physicians deemed that penicillin was the best and only treatment option.

However, the patient endorsed a history of penicillin allergy. At 22 years of age, she was prescribed amoxicillin for an upper respiratory infection. Thirty to 60 minutes after the first dose, she developed diaphoresis and dyspnea and felt like her “windpipes were closing in.” She denied skin, cardiovascular, or gastrointestinal symptoms. She recalled that she did not seek medical attention and her symptoms resolved overnight, but it is unclear whether she took medications to relieve symptoms. She had a penicillin skin prick test and an intradermal skin test in the same year at an allergist's office; based on these test results, she was instructed to

strictly avoid penicillin and related antibiotics in the future. She denied any history of Stevens-Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, or toxic epidermal necrolysis syndrome and did not have any other drug allergies, asthma, allergic rhinitis, or atopic dermatitis.

The patient was cared for by the high-risk obstetrics team and a multidisciplinary conference was held to coordinate her care. The care teams discussed the possibility of penicillin skin testing to evaluate if she may have “outgrown” the penicillin allergy, which may be a reasonable approach in the clinical context of pregnancy and a remote reaction or unconvincing history of penicillin allergy. However, given that the pregnancy in this patient was deemed high-risk (due to tertiary syphilis infection and advanced maternal age) and that she provided a history concerning for immediate hypersensitivity to penicillin, the decision was made to forego the risks of testing and challenge and proceed directly with penicillin desensitization to initiate treatment. The patient consented to the risks of the procedure, which was carried out in the intensive care unit with 1:1 critical care nursing present, the obstetric team on standby, fetal monitoring, and emergency anaphylactic medications at the bedside. A 15-step protocol based on the published literature on penicillin desensitization techniques was used.^{1–5} She tolerated the desensitization protocol to the treatment dose of penicillin at 1,000,000 U/h for presumed neurosyphilis. She remained in the hospital for 14 days to complete intravenous treatment and was discharged home without complication.

Introduction

The prevalence of patient-reported penicillin allergy in the US population is estimated to be as high as 10% and even higher in hospitalized patients.^{1,5–8} After formal drug allergy evaluation with testing, most of these patients are found not to be allergic to penicillin and can safely tolerate the drug.^{5,6} As this case illustrates, there are still certain situations in which a patient has evidence of

IgE-mediated allergy (based on a suggestive history and/or testing) and are in need of penicillin. Syphilis in pregnancy is a classic example of this, and Centers for Disease Control and Prevention (CDC) reports show that rates of syphilis infection are increasing in the United States.⁹ As such, desensitization (induction of drug tolerance) is an important service to provide for patients with penicillin allergy.

In this review, we explore the approach to identifying patients appropriate for desensitization and delineate the procedure, with particular attention to performing it during pregnancy. We also discuss the recent movement within the field of medicine to proactively clarify penicillin allergy, an approach that could decrease the number of patients with questionable penicillin allergy.

Syphilis During Pregnancy

Syphilis in pregnancy, caused by *Treponema pallidum*, carries a risk of transplacental transmission of the infection to the fetus. Congenital infection can lead to perinatal death, premature delivery, congenital anomalies, and serious long-term sequelae in the infants, such as deafness.¹⁰ The incidence of congenital syphilis has increased by 38% from 8.4 to 11.6 cases per 100,000 live births from 2012 to 2014.⁹ The CDC recommends that all pregnant women be screened for syphilis at the first prenatal visit, with repeat screening during the third trimester and at the time of delivery for women who are at high risk for syphilis.¹¹ A nontreponemal test, such as the rapid plasma reagin test or the Venereal Disease Research Laboratory test is used for screening. These tests detect the presence of nonspecific antibodies released during syphilis infection and have low specificity. A treponemal test, such as fluorescent treponemal antibody absorption, is used as the confirmatory step by detecting antibodies against treponemal antigens. Pregnant women with seropositivity are considered actively infected if there is no documentation of adequate treatment received previously. According to the CDC, “Penicillin G is the only known effective antimicrobial for preventing maternal transmission to the fetus and treating fetal infection. Pregnant women should be treated with the penicillin regimen appropriate for their stage of infection.”¹¹

Penicillin Allergy Evaluation

Given the frequency with which penicillin allergy is reported, it is not uncommon to encounter pregnant women with a reported penicillin allergy. The cornerstone for penicillin allergy evaluation is a thorough history, with special attention to the timing of symptoms, temporal relation to drug administration, and history of tolerance to related compounds. Reactions to penicillin can occur through different mechanisms; our discussion focuses on the identification and management of type 1 IgE-mediated reactions.^{2,12}

In type 1 hypersensitivity reactions to penicillin, the immune response is targeted against new antigenic determinants that are formed when penicillin degrades and binds to carrier proteins.² The major determinant and minor determinants are formed from the β -lactam core ring.² Some patients have IgE antibodies directed at R-group side chains; however, this is less commonly seen in the United States.^{5,13,14} Introduction of penicillin to a previously sensitized patient triggers IgE-sensitized mast cells and basophils to release proinflammatory mediators that cause symptoms of an allergic reaction (eg, urticaria, angioedema, dyspnea). This can range in severity from mild reactions to life-threatening anaphylaxis.^{1,2} Symptoms typically begin immediately after or soon after exposure to the drug.

Readministration of penicillin to patients with IgE-mediated allergy can lead to potentially severe hypersensitivity reactions, including anaphylaxis and death. These patients should be

managed with caution and given penicillin, if it is required, using desensitization protocols. However, many patients with self-reported penicillin allergy have lost their sensitivity over time or might have had an initial incorrect diagnosis. Skin testing and oral challenges in these cases can be helpful in confirming lack of allergy. Penicillin skin testing with major and minor determinants can reliably detect patients at risk for IgE-mediated reactions.^{2,5,6,15} Skin testing with Pre-Pen (containing penicilloyl-polylysine, the major determinant; ALK-Abellø, Hørsholm, Denmark) and penicillin G (containing benzylpenicillin, one of the minor determinants) appears to have a very high negative predictive value, reported to be greater than 95%.^{2,4–6,12,16} Because the predictive value is not 100% and there are other minor determinants that can account for severe reactions, an oral challenge with penicillin or amoxicillin is typically performed before removal of the penicillin allergy label.^{5,6,17} Patients with positive skin test reactions should avoid penicillin in the future or undergo desensitization if penicillin treatment is necessary and they are suitable candidates.⁵

Penicillin Allergy Evaluation in Pregnancy

In general, it is preferable to avoid drug testing during pregnancy when possible. However, there can be situations such as syphilis in pregnancy that warrant special consideration of methods to safely introduce the drug. According to the CDC, “Pregnant women who have a history of penicillin allergy should be desensitized and treated with penicillin. Skin testing or oral graded penicillin dose challenge might be helpful in identifying women at risk for acute allergic reactions.”¹¹ The data on the safety and utility of penicillin skin testing during pregnancy is limited. In a study published in 2006 by Macy,¹⁸ 56 pregnant women with group B streptococcus colonization were recruited for penicillin skin testing (without oral challenge). Of these, 2 patients (4%) had mild adverse reactions from skin testing. Of the 53 patients with negative skin test results, 47 (89%) subsequently received at least 1 course of penicillin intrapartum for group B streptococcus prophylaxis; 2 patients developed delayed-onset rashes attributable to the use of intrapartum penicillin. Based on their findings, Macy suggested that penicillin skin testing in pregnant women could be safely performed. In a 1985 study by Wendel et al³ of 15 pregnant women who had positive penicillin skin test reactions and were subsequently desensitized, 14 underwent uneventful skin testing, but 1 of these patients, who had secondary syphilis, developed flushing, pruritus, and wheezing with cutaneous penicillin skin testing requiring treatment with epinephrine. Therefore, potential adverse reactions with skin testing should be prepared for with a team equipped to promptly recognize and treat symptoms. As we discuss below in more detail, there also are a few case series of penicillin desensitization being performed during pregnancy. Decisions for penicillin testing, challenge, and desensitization during pregnancy will depend on many factors, including the severity of prior reactions, maternal infection and comorbidities, and estimation of risk.

Indications for Penicillin Drug Desensitization

Penicillin desensitization has been performed for more than 50 years and is the preferred modality of drug administration in patients with penicillin allergy for whom penicillin is identified as the best and only treatment option without suitable alternative.¹⁹ The classic example of this, as discussed, is syphilis during pregnancy.^{3,10} Other situations can arise, such as infections with multidrug-resistant organisms that are susceptible only to penicillins or some diseases that are optimally treated with penicillins, such as certain cases of endocarditis and listeriosis.^{3,12} The desensitization approach is typically used in patients with

confirmed penicillin allergy and/or a history that strongly suggests an IgE-mediated allergy. It also is used in situations in which the risk of skin testing and oral challenge might be deemed too high or such testing is not an option.^{1,5,20} Due to the availability of alternative drugs in most situations, penicillin desensitization does not appear to be performed with high frequency. However, because the situations described earlier necessitating penicillin use can arise, penicillin desensitization is an important service to offer.

Penicillin desensitization is generally not recommended in patients with poorly controlled asthma (forced expiratory volume in 1 second <70% of their predicted value), unstable vital signs, or active cardiac disease.²⁰ Desensitization is contraindicated in patients who have had significant life-threatening reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis syndrome, drug reaction with eosinophilia and systemic symptoms, or immuno-cytotoxic reactions.^{1,6,20} It also is not recommended for non-IgE-mediated reactions to penicillin.²¹

Penicillin Desensitization Procedure

Drug desensitization is a procedure that modifies the patient's immune response to promote unresponsiveness rather than hypersensitivity to a particular drug.^{1,2,20} Desensitization protocols are commonly used for introducing specific medications to patients with drug allergy, such as antibiotics, aspirin, and chemotherapeutic agents. It is believed that repeated administration of sub-threshold doses of the drug provides enough antigenic determinants to bind IgE on the surface of basophils and mast cells without cross-linking, rendering these cells unresponsive to higher doses of the drug.^{2,5,20} The desensitized state is maintained as long as the drug is continued and is lost at drug discontinuation.^{2,5,20}

Protocols for penicillin desensitization are available in oral and intravenous formulations.^{1,3,4,12} Oral and parenteral routes appear to provide effective desensitization, but oral routes can have variable absorption rates.^{2,22} Usual protocols for intravenous penicillin start at a diluted dose, commonly 1:10,000 of the target dose.^{1,3,5,20} The dose given is determined by the concentration of the solution and the rate at which the infusion pump is set. The general approach to desensitization procedures involves doubling the dose every 15 minutes using a continuous infusion until the target dose is achieved.^{1–4} Published protocols range in the number of steps, typically from 12 to 16 steps, to achieve desensitization.^{1,3–5} The β -blockers are typically held before desensitization.

During the desensitization procedure, if there is no adverse reaction, the next step is initiated. For mild reactions, the infusion is typically held and once the reaction has been successfully treated, the protocol is resumed by repeating the step at which the reaction occurred.^{3,5} In the literature, mild reactions were reported in 30% to 80% of patients who underwent penicillin desensitization.^{3,20,23} In most cases, reactions can be managed with medications and the protocol can be successfully resumed.^{3,20}

It is important to have staff trained and comfortable in administering desensitization protocols and identifying reactions. In addition, medications to treat anaphylaxis should be readily available.²⁰ The setting and level of care in which the procedure is performed depend on many factors, including the severity of past reactions, patient comorbidities, hospital protocols, staff training, and staff comfort levels. Although oftentimes antibiotic desensitization occurs in the intensive care unit setting, many articles have described the ability to perform these procedures successfully, as many experienced centers do, in an outpatient setting.^{1,2,20} After desensitization, penicillin therapy should be given without interruption until completion. In this case of presumed neurosyphilis, the dosing options were continuous intravenous infusion or dosing every 4 hours for a total of 14 days. If a patient misses doses that lead to clearing of the medication from the system or if penicillin is

needed again in the future, then the desensitization procedure should be repeated.¹²

Of note, in patients with syphilis, treatment with penicillin can trigger a Jarisch-Herxheimer reaction. Upon treatment with penicillin, death of spirochetes can release endotoxins and lipoproteins, products that are believed to trigger this syndrome. Symptoms of the Jarisch-Herxheimer reaction can include fevers, chills, myalgias, flushing, and worsening of existing skin rash. These symptoms typically begin at 4 hours after initiation of penicillin therapy, peak at 8 hours, and subside by 16 hours.²⁴ Symptoms of a Jarisch-Herxheimer reaction tend to persist for longer duration than those of an allergic reaction.^{10,24} It is important to be aware of this reaction, which can sometimes be mistaken for a drug reaction.

Penicillin Desensitization in Pregnant Women

The literature on desensitization during pregnancy consists of small case reports and series that have described pregnant women with penicillin allergy who successfully completed penicillin desensitization protocols and subsequently received penicillin therapy for the treatment of severe infections.^{3,10,15,22} Much of the limited literature on penicillin desensitization during pregnancy is from the 1980s and 1990s. In 1985, Wendel et al³ described one of the first published series of successful penicillin desensitization in pregnant women. Fifteen pregnant women with penicillin allergy confirmed by skin testing, 13 of whom had syphilis infection, were desensitized to penicillin with a protocol that administered increasing doses of oral penicillin V. At completion the women were given full-dose parenteral penicillin G or ampicillin. Approximately one third of these patients developed mild allergic symptoms, such as generalized pruritus and/or urticaria, and all 15 women successfully completed the protocol.^{3,5} The investigators concluded that pregnant women with penicillin allergy and serious infections can undergo an oral desensitization procedure with an acceptable level of safety to receive penicillin therapy.

In 1986, Ziaya et al¹⁰ published a case report that described a pregnant woman who was successfully desensitized in the intensive care unit using an intravenous protocol during her second trimester. The investigators suggested that advantages of intravenous desensitization protocols include easier dosage control and the ability to quickly halt a dose if a reaction were to occur. Chisholm et al²² in 1997 examined the use of oral vs intravenous desensitization regimens in pregnant women. This retrospective study looked at 11 oral desensitization procedures and 6 intravenous procedures; the 2 procedures were deemed to be equally effective in achieving desensitization. In addition, there were no significant differences between patients in duration of time in a monitored bed and length of hospital stay.

Although the literature is limited, these case series suggest that penicillin therapy can be given to pregnant women with penicillin allergy and serious infections with an acceptable level of safety by using desensitization procedures. The goal of therapy is to cure serious maternal infections. Allergic reactions can occur with testing and desensitization protocols; this can present unique risks to the pregnant woman and the fetus. Thus, close monitoring is imperative to promptly diagnose and treat an allergic reaction if one were to occur.

Proactive Clarification of Penicillin Allergy

The desensitization approach is typically used in patients with confirmed penicillin allergy and/or a history concerning for IgE-mediated allergy. It also is used in situations in which the risk of skin testing and oral challenge is deemed too high or when such testing is not possible. However, penicillin allergy is vastly over-reported. It has been reported that, after formal allergy evaluation and testing, approximately 90% of patients with self-reported

penicillin allergy can safely receive penicillin.^{5–7} There is a growing body of literature that shows that a penicillin allergy label is associated with higher rates of broad-spectrum antibiotic use, colonization and infection with drug-resistant organisms, and higher health care usage and costs.^{8,25–30} As such, consensus guidelines and position papers advocate for allergy evaluation of patients with a questionable history of IgE mediated hypersensitivity to penicillin.^{5,31} Increasingly, protocols and clinical pathways are being implemented to facilitate penicillin allergy clarification.^{5,7} The trend in recent years to evaluate penicillin allergy proactively with skin testing and oral challenges while the patient is healthy will help decrease the number of patients incorrectly labeled as “penicillin allergic.” This in turn could decrease the frequency with which we contemplate testing, challenges, and desensitizations in an acute setting.

Conclusion

In those patients with IgE-mediated allergy in need of penicillin therapy, penicillin desensitization is an important service to provide. As described in this clinical scenario and several published case series, desensitization protocols have been used to achieve successful desensitization in pregnant women who require penicillin therapy to cure serious maternal infections. Allergic reactions, mostly mild, can occur in approximately one-third or more of patients undergoing desensitization procedures.^{3,4,20} As such, it is important that close monitoring be observed, with prompt recognition of allergic reactions and treatment administered by experienced staff.

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