



Effectiveness and safety of an algorithm for the treatment of pregnant women with syphilis and a history of penicillin allergy

Arq Asma Alerg Imunol. 2023;7(4):425-7.
<http://dx.doi.org/10.5935/2526-5393.20230063-en>

Science provides vast opportunities for academic advancement and is essential for the development of any society. Thanks to the daily encouragement I received during my training as an allergist and immunologist, I had the great honor of presenting my master's thesis, "Algorithm for treatment of pregnant women with syphilis and history of allergy to penicillin – effectiveness and safety", at the World Allergy Congress (WAC) 2023, held by the World Allergy Organization in Thailand. The WAC had 148 speakers and 1,336 participants from 57 countries, and our study was the only one conducted outside Asia to win an award for best oral presentation.

In addition to the academic importance it holds for the first author personally, this work should be socially relevant as well, given its contribution to patients who have enrolled in the study and those who will enroll in future.

During pregnancy, syphilis treatment must be started immediately after a positive (reactive) test, regardless of the type of test or the titer detected. Immediate treatment should also be initiated in cases where there is no clear confirmatory evidence of infection and in pregnant women who have had sexual contact with a person known to have syphilis. Congenital syphilis is a preventable condition, provided the infection is detected during pregnancy (through effective prenatal care) and treated appropriately.¹⁻⁶

The only effective treatment for gestational syphilis is administration of benzathine penicillin (BP), which is bioavailable to the fetus and thus ensures treatment of both mother and child. It bears stressing that there is no evidence of resistance of *T. pallidum* to penicillin in Brazil or elsewhere in the world, and that the first-line treatment of choice for syphilis in non-pregnant patients also involves penicillin antibiotics. The Brazilian Ministry

of Health recommends that all pregnant women with a proven allergy to benzathine penicillin be referred to a specialized tertiary care center for desensitization in accordance with existing protocols.^{2,3,5}

Penicillins are among the most common causes of drug-induced allergy. Reactions can manifest as a wide range of clinical conditions, from mild rash, urticaria, or angioedema to full-blown anaphylaxis.⁷ However, the consequences of penicillin allergy mislabeling (PAM) are well documented and occur at both the individual and public-health levels.⁸ Pregnant women also experience adverse health effects associated with self-reported penicillin allergy, including increased risk of cesarean section and increased length of hospital stay.⁹ PAM must therefore be viewed as a threat to individual and public health, and detailed clinical histories must be obtained from all patients with alleged reactions to a penicillin antibiotic.¹⁰

The purpose of the detailed clinical history is to identify patients at high versus low risk of immediate reactions to antibiotics and thus determine how further investigation should proceed. A combination of detailed clinical history assessment with *in vivo* and *in vitro* testing is the safest approach to guide penicillin rechallenge.¹⁰

In cases of suspected immediate hypersensitivity reactions, we continue the clinical workup to confirm or rule out the diagnostic hypothesis with the aid of an algorithm. This algorithm involves administering a specific clinical questionnaire developed by the authors (with standardized scoring for previously defined clinical criteria, taking into account: clinical manifestations compatible with an immediate hypersensitivity reaction; first immediate hypersensitivity reaction 10 years or less before the date of assessment; history of exposure/re-exposure to beta-lactam antibiotics), followed by *in vivo* (immediate skin-

prick and intradermal) tests and, if possible, *in vitro* tests (detection of penicillin G-, penicillin V-, and amoxicillin-specific serum IgE).

The combination of a clinical history consistent with an immediate hypersensitivity reaction and positive *in vivo* or *in vitro* test results is diagnostic of penicillin allergy, and the patient must be referred for desensitization. If the clinical history is questionable or inconsistent with immediate hypersensitivity (i.e., suggesting low risk of a further reaction) and both *in vivo* and *in vitro* tests are negative, a drug provocation test can be carried out to confirm or rule out the diagnosis of penicillin allergy.^{2,3,5}

Drug provocation testing is considered the gold standard for ruling out a diagnosis of allergy. Its main objective is de-labeling, given the aforementioned negative implications of PAM, which include heightened risk of antimicrobial therapy failure, antimicrobial resistance, adverse drug reactions secondary to the use of broader-spectrum or alternative antibiotics, and increased health expenditure.¹⁴

Rapid drug desensitization (RDD) is indicated for any immediate hypersensitivity reaction, whether allergic or non-allergic, thus representing an important advance in improving the treatment and prognosis of patients with such reactions.¹¹ RDD is a safe, effective process in which a temporary state of mast-cell and basophil hyporesponsiveness is induced through incremental administration of suboptimal doses of the culprit drug until the desired therapeutic dose is reached.¹² Desensitization allows patients to receive antimicrobial treatment of choice for their infections, and its success has been demonstrated in several clinical studies. To date, there is no universal or consensus drug desensitization protocol for hypersensitivity reactions to beta-lactam antibiotics. Desensitization for BLs must always be performed by specialized teams, led by physicians specializing in allergy and immunology, in a hospital setting with resuscitation equipment readily available.¹¹⁻¹³

Our study has already enrolled approximately 200 pregnant women. Interim analysis of 165 participants identified 81 (49.1%) with a clinical history of high risk for anaphylaxis, all of whom were desensitized; the remaining 84 had a low-risk clinical history and negative skin tests and underwent challenge. Intradermal tests were positive in 11 of 165 patients (6.7%), all with a high-risk clinical history. Positive intradermal tests were significantly associated with the development of reactions during desensitization ($p < 0.0001$). Indeed, only one patient with a negative test reacted during desensitization. Only two patients had positive allergen-specific IgE: one had a reaction to penicillin rechallenge, while the other did not. All 84 patients

(50.9%) considered low-risk were subjected to provocation testing. Only three reacted: two (2.4%) had immediate hypersensitivity reactions, while one had a delayed reaction (1.2%). The diagnosis of penicillin allergy was confirmed in 9.7% of our patients. The algorithm showed 98.8% efficacy, and only two patients could not have their infection treated with penicillin. The overall safety of the algorithm was 92.1%, considering that only 13 patients developed hypersensitivity reactions upon re-exposure to penicillin, 10 of whom had mild reactions.

We invite the readers of AAAI to learn more about this project. Should you be interested in having your department, clinic, or practice participate, we will be happy to answer questions and assist with implementation, as we are seeking to conduct a multicenter study. Science extends far beyond classrooms and laboratory benches, as clinical studies allow us to confirm our hypotheses in a reproducible manner. We hope this message and our study will encourage readers to become investigators.

References

1. Avelleira JCR, Bottino G. Sífilis: diagnóstico, tratamento e controle. *An Bras Dermatol*. 200;81(2):111-26.
2. Brasil. Ministério da Saúde. Protocolo Clínico e Diretrizes Terapêuticas para Prevenção da Transmissão Vertical de HIV, Sífilis e Hepatites Virais [Internet]. 2022. Available from: <https://www.gov.br/aids/pt-br/central-de-conteudo/pcdts>.
3. Brasil. Ministério da Saúde. Protocolo clínico e Diretrizes terapêuticas para infecções sexualmente transmissíveis. Relatório de recomendação do Ministério da Saúde, 2015.
4. Tsimis ME, Sheffield JS. Update on pyphilis and pregnancy. *Birth Defects Res*. 2017;109(5):347-52.
5. Garcia JFB, Aun MV, Motta AA, Castells M, Kalil J, Giavina-Bianchi P. Algorithm to guide re-exposure to penicillin in allergic pregnant women with syphilis: Efficacy and safety. *World Allergy Organ J*. 2021 May 21;14(6):100549.
6. Pinto RM, Valentim RAM, da Silva LF, Lima TGFMS, Kumar V, de Oliveira CAP, et al. Analyzing the reach of public health campaigns based on multidimensional aspects: the case of the syphilis epidemic in Brazil. *BMC Public Health*. 2021;21(1):1632.
7. Doña I, Guidolin L, Bogas G, Olivieri E, Labella M, Schiappoli M, et al. Resensitization in suspected penicillin allergy. *Allergy*. 2023 Jan;78(1):214-24.
8. Ramsey A. Penicillin Allergy and Perioperative Anaphylaxis. *Front Allergy*. 2022 Jun 9;3:903161.
9. Kuder MM, Lennox MG, Li M, Lang DM, Pien L. Skin testing and oral amoxicillin challenge in the outpatient allergy and clinical immunology clinic in pregnant women with penicillin allergy. *Ann Allergy Asthma Immunol*. 2020;125(6):646-51.
10. Shenoy ES, Macy E, Rowe T, Blumenthal KG. Evaluation and Management of Penicillin Allergy: A Review. *JAMA*. 2019;321(2):188-99.
11. Giavina-Bianchi P, Aun MV, Galvão VR, Castells M. Rapid Desensitization in Immediate Hypersensitivity Reaction to Drugs. *Curr Treat Options Allergy*. 2015; 2:268-85.

12. Cardona R, Santamaría L, Guevara-Saldaña L, Calle A. Hipersensibilidad a antibióticos betalactámicos: algoritmos de manejo y desensibilización como alternativa terapéutica vital [Hypersensitivity to β -lactam antibiotics: algorithms of management and desensitization as a vital therapeutic alternative]. *Rev Alerg Mex.* 2021 Jan-Mar;68(1):35-47.
13. Castells MC, Tennant NM, Sloane DE, Ida Hsu F, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol.* 2008;122:574-80.
14. Stone CA Jr, Trubiano J, Coleman DT, Rukasin CRF, Phillips EJ. The challenge of de-labeling penicillin allergy. *Allergy.* 2020;75(2):273-88.

No conflicts of interest declared concerning the publication of this letter.

Bruna Gehlen
Pedro Giavina-Bianchi

Faculdade de Medicina da Universidade de São Paulo,
Department of Clinical Immunology and Allergy -
São Paulo, SP, Brazil.