

Direct Oral Challenge: A Simpler Path for Low-Risk Penicillin Allergy?

Written by The Life Science Feed Editorial Team · Edited by Mara Voss

Penicillin allergy labels are notoriously common, affecting a significant portion of patients needing antibiotic treatment. These labels frequently lead to the use of less effective, broader-spectrum antibiotics, contributing to increased side effects and the pervasive problem of antimicrobial resistance. The imperative to safely delabel these allergies, particularly in inpatient settings, drives ongoing evaluation of diagnostic strategies.¹

KEY TAKEAWAYS

- **The Pivot:** Direct oral challenge is noninferior to penicillin skin testing for low-risk penicillin allergy evaluation, offering a simpler approach.
- **The Data:** Both methods share the common goal of safely delabeling penicillin allergies to optimize antibiotic prescribing.
- **The Action:** Clinicians should consider direct oral challenge for low-risk patients, especially in settings where specialized skin testing resources are limited.

Penicillin allergy labels are a persistent thorn in the side of antibiotic stewardship, impacting individual patient outcomes and carrying broader public health implications. These mislabels often steer clinicians toward alternative antibiotics, which are frequently less effective, carry higher side effect profiles, and exacerbate antimicrobial resistance.^{1,2,3} The goal is clear: safely remove these labels to ensure patients receive optimal, first-line penicillin-based therapies when appropriate. Two main diagnostic approaches dominate this effort: penicillin skin testing and direct oral challenge.^{1,2,3} The choice between these strategies is not arbitrary; it hinges on a careful stratification of patient risk, the availability of specialized resources, the training and comfort level of healthcare providers, and patient preferences. Penicillin skin testing has long been considered the historical criterion standard for all-risk phenotypes, boasting an excellent safety record. But it demands specialized training and specific resources, which are not universally available. Direct oral challenge, by contrast, is a simpler procedure and has demonstrated noninferiority in low-risk patient populations. But it carries an increased risk if patient selection is not rigorously performed.^{1,2,3}

The Inpatient Dilemma: Skin Testing vs. Direct Oral Challenge

The inpatient setting presents a particularly acute need for efficient and safe penicillin allergy evaluation, given the high utilization of antibiotics in hospitalised patients. McDanel, Mitri, and Li explored the pros and cons of penicillin skin testing versus direct oral challenge specifically within this environment, highlighting the practical challenges and benefits of each.¹ They noted that widespread and routine penicillin allergy evaluation in inpatient care is integral for successful antibiotic stewardship, but the method matters.¹

Penicillin skin testing, while historically robust, requires a dedicated allergy specialist, specific reagents (penicilloyl-polylysine and penicillin G), and the capacity to manage potential systemic reactions. This often means a referral to an allergist, which can delay antibiotic optimisation, especially in a busy inpatient service. The process involves intradermal injections and observation periods, demanding time and trained personnel.¹

Direct oral challenge, for carefully selected low-risk patients, bypasses these requirements. A low-risk patient typically presents with a remote history of a mild, non-anaphylactic reaction, such as a rash that occurred many years ago, or a family history of penicillin allergy without a personal history. The procedure involves administering a therapeutic dose of penicillin or amoxicillin orally, often in a single dose, under observation. If no reaction occurs within a specified period, the allergy label is removed. This approach can be integrated into general medical wards with appropriate protocols and staff education, making it more accessible.¹

Navigating Penicillin Allergy in Pregnancy

The complexities of penicillin allergy evaluation are further amplified in pregnant patients, where antibiotic choices have implications for both mother and fetus. Belmont, Li, and Tsao addressed this specific population, comparing direct challenges to penicillin skin testing in pregnancy.² Mislabelled penicillin allergies in pregnant women can lead to the use of alternative antibiotics, which may have less favorable safety profiles during gestation or be less effective against common pregnancy-related infections, such as Group B Streptococcus.²

The authors reiterated that both skin testing and direct oral challenge aim to safely delabel allergies, but their application in pregnancy requires careful consideration. Skin testing, while safe, still carries the logistical hurdles of specialized resources. Direct oral challenge, when applied to low-risk pregnant patients, offers a streamlined pathway. The critical aspect remains rigorous patient selection to minimise any potential risk to the mother or fetus.²

A randomized trial by Patrawala, Mustafa, and Kraude specifically compared direct challenges to penicillin skin testing for outpatient low-risk penicillin allergy evaluations in pregnancy.³ This study provided direct comparative data, which is essential for guiding clinical practice in this vulnerable population. The trial design aimed to determine if the simpler direct oral challenge was truly noninferior to the traditional skin testing method in terms of safety and efficacy for delabeling.³

The Numbers on Delabeling

While specific quantitative outcomes like delabeling rates or adverse event rates were not detailed in the provided abstracts, the consistent message across all three papers is that direct oral challenge is noninferior in low-risk patients.^{1,2,3} This noninferiority is a significant finding, as it implies that a simpler, less resource-intensive method can achieve the same clinical outcome as the more complex, traditional approach for a significant subset of patients. The primary goal for both methods is to safely remove the penicillin allergy label, thereby optimising antibiotic prescribing and reducing reliance on broader-spectrum agents.^{1,2,3}

The safety record of penicillin skin testing is excellent, making it the historical gold standard. But the logistical demands often limit its widespread application. Direct oral challenge, while simpler, requires meticulous patient selection to maintain a comparable safety profile. The risk of an adverse reaction, though low in carefully screened low-risk patients, is still a consideration. Clinicians must weigh the benefits of a streamlined process against the potential for an immediate reaction, however rare.^{1,2,3}

For example, in the outpatient setting, particularly for pregnant patients, the ability to perform a direct oral challenge without needing a specialist referral can significantly reduce delays in care and improve patient access to appropriate antibiotics. This is especially relevant for conditions where timely antibiotic administration is essential for patient outcomes, such as urinary tract infections or Group B Strep prophylaxis. The efficiency of oral administration is a key factor here.

The Catch: Rigorous Patient Selection

The consistent caveat across all discussions of direct oral challenge is the absolute necessity of rigorous patient selection.^{1,2,3} This is not a procedure for every patient with a penicillin allergy label. Patients with a history of severe reactions, such as anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms (DRESS), are unequivocally high-risk and require specialist evaluation, typically involving skin testing and potentially graded challenges in a controlled environment.¹

Defining "low-risk" is paramount. It generally includes patients whose reported reaction was remote (e.g., more than 10 years ago), mild (e.g., a non-urticarial rash without respiratory compromise), or vague (e.g., "upset stomach"). A thorough history is the cornerstone of this risk stratification. Without it, the direct oral challenge carries increased risk. The importance of accurate historical data cannot be overstated in allergy assessment.

The availability of resources also dictates the feasibility of each approach. In settings where allergists are scarce, or where rapid delabeling is needed for inpatient management, direct oral challenge, if safely implemented, offers a practical solution. This requires education and training for general practitioners and hospitalists to confidently identify low-risk patients and manage potential mild reactions. The Oxford Handbook of Infectious Diseases and Microbiology provides practical guidance on antimicrobial therapy, which would include appropriate allergy assessment.

Implications for Antibiotic Stewardship

The broader implication of validating direct oral challenge for low-risk patients extends directly to antibiotic stewardship programs. Mislabelled penicillin allergies are a major driver of suboptimal antibiotic prescribing, leading to increased use of fluoroquinolones, cephalosporins, and vancomycin. These alternatives often have broader spectra, higher costs, and greater propensity to induce resistance or cause *C. difficile* infection.¹

By safely delabeling more patients, clinicians can revert to narrower-spectrum, highly effective, and generally well-tolerated penicillins, such as amoxicillin or penicillin G. This not only benefits the individual patient by providing optimal therapy but also contributes to public health by reducing the selective pressure that drives antimicrobial resistance. The ability to perform these evaluations more routinely, especially in inpatient settings, is a significant step forward for antibiotic stewardship initiatives.¹

Still, the implementation of direct oral challenge programs requires careful planning. Protocols must be clear, staff must be trained, and emergency medications for anaphylaxis must be readily available. While the risk is low in selected patients, it is never zero. The balance between accessibility and safety is delicate, but the evidence supports direct oral challenge as a viable, noninferior option for low-risk individuals. This approach could significantly improve patient care and public health outcomes by making penicillin allergy delabeling more routine and less burdensome. The ongoing debate around oral drug safety underscores the need for careful patient selection in all oral challenges.

CLINICAL IMPLICATIONS

The consistent message that direct oral challenge is noninferior to skin testing for low-risk penicillin allergy labels should prompt a re-evaluation of current practice. For many GPs and specialists, the logistical hurdles of skin testing have meant that penicillin allergy labels often persist unchallenged, leading to suboptimal antibiotic choices. This evidence provides a clear pathway to safely delabel a significant portion of these patients, improving access to first-line therapies.

Clinicians must, however, internalise the absolute necessity of rigorous patient selection. "Low-risk" is not a casual designation; it demands a thorough history to rule out any severe or recent reactions. Without this diligence, the perceived simplicity of direct oral challenge could lead to avoidable adverse events, undermining confidence in the approach.

The broader impact on antibiotic stewardship is undeniable. Shifting patients back to penicillins where appropriate means less reliance on broader-spectrum agents, which directly combats antimicrobial resistance and reduces the incidence of associated side effects. This is a win for individual patients and for public health, making the effort to implement direct oral challenge protocols well worth it.

EDITORIAL & AI STANDARDS

AI tools are used solely to structure and summarise evidence from peer-reviewed primary sources. No AI-generated conclusions appear in The Life Science Feed without editor verification against the primary source.

REFERENCES

1. McDanel DL, Mitri EA, Li JT. Inpatient Penicillin Allergy Evaluation-Skin Testing Versus Direct Oral Challenge? J Allergy Clin Immunol Pract. 2026.
2. Belmont AP, Li L, Tsao LR. One Allergy, Two Paths: Navigating Penicillin Allergy Evaluation in Pregnant Patients, Direct Challenges Versus Penicillin Skin Testing in Pregnancy. J Allergy Clin Immunol Pract. 2026.
3. Patrawala S, Mustafa SS, Kraude R. A Randomized Trial Comparing Direct Challenges to Penicillin Skin Testing for Outpatient Low-Risk Penicillin Allergy Evaluations in Pregnancy. J Allergy Clin Immunol Pract. 2025.

LICENCE & RIGHTS

© 2026 The Life Science Feed. All rights reserved. This content is produced for medical education purposes. It may not be reproduced, distributed, or transmitted without prior written permission from The Life Science Feed.

MEDICAL DISCLAIMER

This content is intended for healthcare professionals only and does not constitute medical advice. Clinical decisions must be made by qualified practitioners based on individual patient circumstances.

FOLLOW THE LIFE SCIENCE FEED

Instagram @lifesciencefeed **LinkedIn** linkedin.com/company/thelifesciencefeed

thelifesciencefeed.com