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Avaliação de teste cutâneo de contato quanto à capacidade de identificação etiológica de eritema pigmentar fixo: revisão sistemática e meta-análise

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Orientador: Prof. Renan Rangel Bonamigo

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Ao meu marido, meu principal apoio nos últimos 14 anos da minha jornada acadêmica. Aos meus pais, que são minhas referências na medicina e na vida. E, primordialmente, à minha filha: dedico a você esta conquista, para que cresça sabendo que o mundo lhe pertence e que o lugar de uma mulher é onde ela desejar estar.

Resumo da Tese

INTRODUÇÃO: O eritema pigmentar fixo (EPF) é uma farmacodermia com lesões recorrentes no mesmo local após reexposição ao fármaco. Embora o teste de provocação oral (TPO) seja o padrão-ouro, envolve riscos de reativação sistêmica e dilemas éticos. Testes cutâneos, como *patch test* e provocação tópica aberta (ROAT), surgem como alternativas seguras, contudo carecem de padronização e evidências de acurácia comparadas ao TPO.

OBJETIVOS: Avaliar se o *patch test* e a provocação tópica possuem acurácia e segurança para substituir o TPO no diagnóstico do EPF, estimando sensibilidade e especificidade combinadas e analisando variáveis de positividade.

METODOLOGIA: Revisão sistemática e meta-análise (modelo PICO) nas bases MEDLINE, Embase, LILACS, Scopus e Web of Science (desde 1972). Incluíram-se estudos comparando testes cutâneos ao TPO no EPF. A qualidade foi avaliada pelo QUADAS-2 e a síntese quantitativa utilizou modelos Bayesianos bivariados para estimar a performance diagnóstica e a curva SROC.

RESULTADOS: Incluíram-se 78 estudos, com 225 intervenções em 145 pacientes. A performance foi superior em pele lesional ($p < 0,001$), com sensibilidade de 20,6% e positividade de 19,2%, contra 15,4% e 5,0% em pele não lesional [OR: 7,05 (IC 95%: 2,03–24,39)]. Variáveis técnicas e farmacológicas influenciaram o desempenho: houve maior positividade com uso de DMSO (100%) e no intervalo de duas semanas após resolução [Sensibilidade: 45,0%; Especificidade: 94,7%; OR: 14,72 (IC 95%:

1,78–121,2)]. Também houve maior reatividade para anticonvulsivantes (68,8%), excipientes (57,9%) e metabólitos (100%). O perfil de segurança foi favorável, com raras reações sistêmicas.

CONCLUSÃO: Os dados desta revisão devem ser interpretados com cautela, dadas as limitações metodológicas da literatura disponível. Testes cutâneos são úteis, especialmente sobre a pele lesional, mas apresentam desempenho inferior ao TPO. Evidências sinalizam a necessidade de novos estudos prospectivos para padronizar fatores técnicos e permitir aplicação clínica mais assertiva e segura, especialmente quanto ao intervalo de testagem e ao veículo.

Palavras-chave: Eritema Pigmentar Fixo; Farmacodermia; Teste de Contato; Teste de Provocação Oral; Revisão Sistemática.

Objetivos de Desenvolvimento Sustentável (ODS) relacionados: Saúde e bem-estar: Garantir o acesso à saúde de qualidade e promover o bem-estar.

Abstract

INTRODUCTION: Fixed drug eruption (FDE) is characterized by recurrent lesions at the same site upon re-exposure to the causal drug. Although the oral provocation test (OPT) is the gold standard, it involves risks of systemic reactivation and ethical dilemmas. Skin tests, such as patch tests and the repeated open application test (ROAT), emerge as safer alternatives; however, they lack standardization and evidence of accuracy compared to OPT.

OBJECTIVES: To evaluate whether patch tests and topical provocation have sufficient accuracy and safety to replace OPT in FDE, estimating combined sensitivity and specificity and analyzing variables related to positivity.

METHODOLOGY: Systematic review and meta-analysis (PICO model) in MEDLINE, Embase, LILACS, Scopus, and Web of Science (since 1972). Studies comparing skin tests to OPT in FDE were included. Quality was assessed by QUADAS-2, and quantitative synthesis used bivariate Bayesian models to estimate diagnostic performance and the SROC curve.

RESULTS: 78 studies were included, totaling 225 interventions in 145 patients. Performance was superior on lesional skin ($p < 0.001$), with 20.6% sensitivity and 19.2% positivity, versus 15.4% and 5.0% on non-lesional skin [OR: 7.05 (95% CI: 2.03–24.39)]. Technical and pharmacological variables influenced performance: higher positivity was observed using DMSO (100%) and a two-week testing interval after resolution [Sensitivity: 45.0%; Specificity: 94.7%; OR: 14.72 (95% CI: 1.78–121.2)]. There was also higher reactivity for

anticonvulsants (68.8%), excipients (57.9%), and metabolites (100%). The safety profile was favorable, with rare systemic reactions reported.

CONCLUSION: Data from this review should be interpreted with caution, given methodological limitations of available literature. Skin tests are useful, especially on lesional skin, but still perform inferiorly to OPT. Evidence highlights the need for new prospective studies to standardize technical factors and allow a more assertive and safe clinical application, especially regarding testing interval and vehicle.

Keywords: Fixed Drug Eruption; Drug Eruption; Patch Tests; Oral Provocation Test; Systematic Review.

Objetivos de Desenvolvimento Sustentável (ODS) relacionados: Saúde e bem-estar: Garantir o acesso à saúde de qualidade e promover o bem-estar.

Lista de abreviaturas

AAAAI: Sociedade Americana de Alergia, Asma e Imunologia (*American Academy of Allergy, Asthma & Immunology*)

AINEs: Anti-inflamatórios Não Esteroides

DMSO: Dimetilsulfóxido

DRESS: Erupção Cutânea com Eosinofilia e Sintomas Sistêmicos (*Drug Reaction with Eosinophilia and Systemic Symptoms*)

EPF: Eritema Pigmentar Fixo

FISARD: Investigadores Franceses de Reações Adversas Cutâneas a Medicamentos (*French Investigators for Skin Adverse Reactions to Drugs*)

ICDRG: *International Contact Dermatitis Research Group*

IgE: Imunoglobulina E

LILACS: Literatura Latino-Americana e do Caribe em Ciências da Saúde

MeSH: Termos de Cabeçalhos de Assuntos Médicos (*Medical Subject Headings*)

NET: Necrólise Epidérmica Tóxica

OMS: Organização Mundial da Saúde

PEGA: Pustulose Exantemática Generalizada Aguda

PICO: População, Intervenção, Comparador e Desfecho (*Population, Intervention, Comparator, Outcome*)

QUADAS-2: Ferramenta para Avaliação da Qualidade de Estudos de Acurácia Diagnóstica (*Quality Assessment of Diagnostic Accuracy Studies 2*)

RAD: Reações Adversas a Drogas

ROAT: Provocação Tópica Aberta Repetida (*Repeated Open Application Test*)

SPSS: *Statistical Package for the Social Sciences*

SROC: Curva Característica de Operação do Receptor Sumarizada (*Summary Receiver Operating Characteristic*)

SSJ: Síndrome de Stevens-Johnson

TC: Teste Cutâneo de Contato (*Patch Test*)

TPO: Teste de Provocação Oral (*Oral Provocation Test*, OPT)

SUMÁRIO

1. REFERENCIAL TEÓRICO

1.1. Reações adversas a drogas: conceitos e classificações

As reações adversas a drogas (RAD) incluem quaisquer respostas a drogas que são nocivas e ocorre em doses normalmente utilizadas para profilaxia, diagnóstico ou tratamento de uma doença ou para a modificação de uma função fisiológica [1,2].

As RAD podem ser classificadas de acordo com o seu mecanismo em duas categorias principais: dose-dependentes e não dose-dependentes[1]. A primeira categoria é relacionada à farmacologia da droga e pode ocorrer em qualquer indivíduo, enquanto a segunda não é relacionada aos efeitos farmacológicos da droga e ocorre somente em indivíduos suscetíveis (sendo clinicamente imprevisíveis).

As reações imprevisíveis são as mais importantes e podem incluir reações de hipersensibilidade imune (alérgica) ou não imune (não alérgica), sendo essas últimas por susceptibilidade genética ou outros mecanismos não definidos, chamados de idiossincráticos[3]. As reações de hipersensibilidade podem representar até um terço das reações adversas às drogas e podem afetar 10-15% dos pacientes hospitalizados[3], sendo uma causa de morbidade importante nesse grupo de pacientes. Essas reações de hipersensibilidade podem ser ainda sub-classificadas como reações alérgicas imediatas, tardias ou retardadas, reações de fotossensibilidade, reações de doenças autoimunes e reações pseudoalérgicas.

As reações alérgicas imediatas, em geral, ocorrem na primeira hora após a administração do medicamento e são mediadas por IgE; já as tardias são medidas por células T e envolvem reações de Gell e Coombs tipo IV [4].

Em 2007, a classificação das RAD foi reelaborada com uma subdivisão em seis categorias: reações tóxicas dose-dependentes (Tipo A); reações não dose-dependentes (Tipo B); reações decorrentes de manifestações tardias decorrentes de resposta farmacológica alternada (Tipo C); efeitos tardios como teratogenicidade ou carcinogênese (Tipo D); sobrecarga da droga por superdosagem ou acúmulo da droga e seus metabólitos (Tipo E); e falha terapêutica esperada (Tipo F)[4].

1.2. Reações cutâneas adversas a drogas: as farmacodermias

A reação cutânea adversa a drogas (farmacodermia) é uma das formas mais frequentes de RAD[5]. É um importante motivo de consultas dermatológicas em pacientes ambulatoriais e internados.

É denominada farmacodermia qualquer efeito indesejável na estrutura ou função da pele, dos anexos cutâneos ou das mucosas ocasionado por medicamentos [6]. As farmacodermias podem ser divididas em graves e não graves. Cerca de 2% de todas as reações cutâneas são denominadas como graves[7]. De acordo com a Organização Mundial da Saúde (OMS), uma farmacodermia é denominada como grave quando resultar em morte, necessitar hospitalização ou longa estadia no hospital, resultar em incapacidade/inaptidão persistente ou significativa ameaçar a vida. Exemplos de reações graves são a anafilaxia, necrose cutânea induzida por anticoagulante, pustulose exantemática generalizada aguda (PEGA), erupção

cutânea com eosinofilia e sintomas sistêmicos (DRESS), erupção medicamentosa fixa generalizada e síndrome de Stevens-Johnson (SSJ) e necrólise epidérmica tóxica (NET). No entanto, as reações mais comuns são as não graves e, entre estas, a erupção exantemática aguda é a mais frequente (até 95% das farmacodermias). Uma reação pouco comum, mas relevante, é o eritema pigmentar fixo (EPF), cuja prevalência estimada é de menos de 1% entre os motivos gerais de consultas dermatológicas ambulatoriais[8].

1.3 Eritema pigmentar fixo: conceitos

O EPF foi descrito pela primeira vez em 1884[9]. Desde então, muitos casos foram descritos associados ao uso de diversos medicamentos. Apesar de não ter uma grande prevalência na população, o EPF pode corresponder de 7 a 21% das erupções medicamentosas[10].

Clinicamente é caracterizado pelo aparecimento único ou múltiplo de lesões arredondadas eritematovioláceas ou acastanhadas na pele. Há uma forma bolhosa e uma não bolhosa[,11,12,13,14]. O surgimento das lesões costuma ser precoce após exposição a medicamentos. No caso de um primeiro quadro clínico reacional à droga, a lesão surge em 8 a 48 horas; no caso de uma reexposição, em 2 a 8 horas[15]. O EPF tem predileção por região genital e peribucal, também podendo ocorrer em tronco e extremidades [16]. A resolução da lesão costuma ocorrer com hiperpigmentação no corpo, mas na região genital pode resolver sem deixar vestígios. A cada reexposição ao medicamento o paciente, além de ter recidiva da farmacodermia no mesmo local, pode ter o surgimento de outras lesões, por isso é importante o

diagnóstico etiológico do fármaco causador da farmacodermia. Apesar de ser uma farmacodermia geralmente localizada, também são descritos casos de formas bolhosas disseminadas semelhantes a casos de farmacodermia graves (particularmente, necrólise epidérmica tóxica) [11,12,16].

Vários medicamentos já foram descritos como possíveis causadores dessa erupção medicamentosa. A frequência na qual cada droga individual causa EPF muda de acordo com região, relacionados com os tipos e a frequência de consumo dos medicamentos. As drogas mais associadas são antibióticos (sulfametoxazol trimetoprim, tetraciclinas, penicilinas, quinolonas e dapsona), anti-inflamatórios não esteróides (AINEs) (ácido acetilsalicílico, ibuprofeno, naproxeno e ácido mefenâmico), paracetamol, barbitúricos, antimaláricos (quinino) e anticonvulsivantes[,17,18]. Outros medicamentos que já foram implicados são o fluconazol e a levocetirizina. Há, também, as descrições de reações cruzadas entre medicamentos[19]. Faltam dados na literatura sobre possíveis drogas causadoras, pois o diagnóstico etiológico nem sempre é possível, principalmente quando o paciente está em uso de múltiplas medicações (polifármácia) e se todas foram iniciadas em períodos iguais ou próximos no tempo.

1.4 Diagnóstico etiológico de farmacodermias

O padrão-ouro para diagnóstico etiológico de farmacodermias, incluindo o EPF, ainda é a reexposição à droga via oral (teste de provocação oral, TPO) [20,21,22,23]. No entanto, há vieses éticos com este procedimento, pelo risco de surgimento de novas lesões e piora dos sintomas e mesmo risco à vida dos

pacientes. No EPF esse tipo de abordagem divide opiniões, tendo em vista ser uma reação localizada e com menores riscos sistêmicos [17].

Apesar de ser o padrão-ouro diagnóstico, não há padronização da forma que o TPO deve ser realizado. Precisam ser estabelecidos vários parâmetros importantes para permitir a reprodução do teste, como a dosagem do medicamento a ser testada e o tempo entre a resolução da lesão ativa e o teste. Dados adicionais sobre segurança e riscos de reações sistêmicas são necessários para que esse teste possa ser implementado na rotina clínica[24].

Outra forma de diagnóstico etiológico é a realização de testes de contato (*patch test*). O teste cutâneo de contato (TC), é um teste *in vivo* e costuma ser o primeiro a ser realizado para o diagnóstico etiológico de farmacodermias não mediadas por IgE, como o EPF, de acordo com as orientações da Sociedade Europeia de Alergia Medicamentosa Cutânea[25,26,27].

Para Sociedade Americana de Alergia, Asma e Imunologia (AAAAI), o TC tem um papel no diagnóstico das farmacodermias por hipersensibilidade tardia. Porém, como os resultados do teste dependem de vários fatores, e há escassa padronização para a sua realização, é indicado de forma rotineira[28].

A forma de realização do TC é estabelecida internacionalmente. Pode ser realizado com a aplicação dos medicamentos a serem testados de forma padrão no dorso do paciente, utilizando-se contensores padronizados. A primeira leitura do teste é costumeiramente realizada 48 horas após a aplicação do medicamento, quando os contensores são retirados; a segunda leitura é realizada em 96 horas (mas a depender do protocolo isso pode ser modificado), e os resultados são interpretados segundo os critérios do *International Contact Dermatitis Research Group* (ICDRG). O teste não deve

ser aplicado nas seguintes situações: uso recente de corticosteróides tópicos ou sistêmicos (7 e 30 dias, respectivamente), uso de imunossupressores, gestação, histórico de anafilaxia, dermatose grave em atividade e exposição solar na região a ser testada nos 7 dias anteriores ao teste[29]. Apesar de ser um teste relativamente não complicado, há diversos entraves para a implementação dele como protocolo diagnóstico de farmacodermias. Em especial quando nos referimos a reações cutâneas à medicamentos, como o EPF. Primeiro, porque a negatividade do teste nem sempre pode excluir que o medicamento esteja relacionado à farmacodermia, sendo possível a ocorrência de falsos negativos[10,30]. Isso se relaciona a uma série de fatores. De uma forma geral, em casos de pacientes com EPF, a testagem em pele não lesional pode causar falsos negativos[27,30,] pois há diferença de reatividade entre pele lesional e não lesional devido a presença de células T de memória [10,12,31,32]; como os testes de contato são geralmente realizados na parte superior do dorso, isso pode gerar resultados falsos negativos[33].

O momento que o TC é realizado também influencia no seu resultado. Atualmente, a recomendação para realização do TC no local de lesões prévias de EPF é realizar pelo menos duas semanas após a resolução das lesões [34].

Outrossim, os pacientes podem não ser sensibilizados ao medicamento original ou o princípio ativo principal, mas sim, aos excipientes ou aos seus metabólitos (os quais são frequentemente não testados) [35]. Na literatura, há descrição de utilização de medicamento puro (com os excipientes) e há descrição do uso da substância prima somente, tornando difícil a padronização. Ainda, em relação aos medicamentos testados, o veículo no qual esses medicamentos são diluídos e são testados na pele também não é padronizado.

Há possibilidade de diluir esses medicamentos em dimetilsulfóxido (DMSO), petrolato e até água[34,36,37]. Também importante, não há uma padronização universal sobre a concentração que cada medicamento deve ser testado. A depender da concentração, alguns medicamentos podem ter efeitos irritativos na pele ou simplesmente não causar reação, sendo mais um motivo pelo qual o teste pode ser falso negativo[10].

Todas essas variáveis descritas podem influenciar na positividade do TC. Na literatura médica é relatada uma taxa de positividade variável, 40-87% dos pacientes com EPF podem positivar o TC a medicamentos[38]. E há dados escassos sobre acurácia devido à não realização padrão da confirmação com o TPO [34,36,39,40].

Além da baixa taxa de positividade relatada e da necessidade de testagem diretamente na lesão para aumentar a acurácia diagnóstica, há uma questão prática relevante: o EPF costuma acometer áreas que são difíceis de realizar um *patch test* oclusivo normal, como a mucosa oral e genital. Por isso, nesses casos, ainda antes da temida provocação oral, tem sido estudada a realização de uma provocação tópica aberta, conhecida como *Repeated Open Application Test* (ROAT)[39]. Historicamente, Alanko *et al.* [41] foram os pioneiros ao demonstrar o valor deste teste aberto no local de lesões residuais em casos em que o *patch test in situ* resultou negativo, utilizando concentrações de 1% a 10% do fármaco. Em suas séries de estudos, a combinação dos testes abertos revelou uma positividade em 81,4% dos pacientes (44 de 54 casos), com reações surgindo poucas horas após a aplicação para substâncias como o salicilato de fenazona e a carbamazepina[41]. A superioridade dessa abordagem reside na sua capacidade de identificar reações precoces que podem passar

despercebidas em leituras convencionais de 48 ou 96 horas do teste epicutâneo tradicional. Outros pesquisadores, como Mahboob *et al.*[42] corroboraram essa eficácia ao demonstrar uma sensibilidade de 91% para o sulfametoxazol a 5% em testes abertos, relatando inclusive casos de reativação de lesões em locais distantes do ponto de aplicação.

Seguindo essa linha de evidências, o grupo francês *French Investigators for Skin Adverse Reactions to Drugs* (FISARD) publicou em 2018 recomendações padronizadas para a execução do ROAT *in situ* no diagnóstico do EPF[43]. O método consiste na aplicação do medicamento sobre um local anteriormente atingido pela farmacodermia, em uma área de aproximadamente 2 cm por 2 cm, uma vez ao dia durante sete dias consecutivos, sem oclusão e com massagem suave para facilitar a absorção. É fundamental que as aplicações sejam interrompidas imediatamente ao surgimento de qualquer eritema, afinal essa estratégia também se mostra com efeitos adversos locais com eritema, indução e até reativação local [41.44.45].

Contudo, em ambos os métodos diagnósticos, tanto o ROAT como TC, ainda há carência de dados robustos que comparem sistematicamente seus resultados ao padrão-ouro, a provocação oral, bem como análises mais detalhadas sobre nuances técnicas relacionadas à sua execução [46,,47]. Faltam informações consistentes acerca das concentrações utilizadas para cada fármaco, dos veículos empregados e de sua relação com positividade verdadeira, diferenciando adequadamente reações específicas de respostas irritativas que podem gerar falsos positivos.

Além disso, os dados disponíveis sobre a segurança desses procedimentos permanecem limitados, especialmente quanto ao risco de

indução de novas lesões de farmacodermia. Embora o TPO seja frequentemente evitado pelo receio de reexposição ao medicamento, também não há informações definitivas sobre os potenciais efeitos adversos associados à realização do TC ou da provocação aberta cutânea em pacientes com EPF. Permanece a incerteza sobre se esses métodos realmente apresentam menor risco de reativação quando comparados entre si.

A principal questão que persiste quanto ao uso de testes cutâneos diagnósticos no EPF é se os resultados negativos podem ser considerados suficientemente confiáveis para permitir a reexposição segura do paciente ao fármaco implicado. São necessárias evidências mais consistentes sobre a sensibilidade desses testes em comparação ao padrão-ouro. Somente com dados metodologicamente sólidos será possível consolidar o teste cutâneo como ferramenta confiável no diagnóstico etiológico das farmacodermias.

A impossibilidade de diagnóstico etiológico causa uma grande morbidade aos pacientes que possuem farmacodermia por causarem mudanças importantes nos tratamentos realizados pelo paciente associada ao potencial de farmacoterapia subótima e reações à reexposição. O TC e a provocação tópica são os métodos mais acessíveis para o diagnóstico etiológico dessas reações medicamentosas. No entanto são necessários mais dados sobre acurácia, segurança/efeitos adversos, padronização das concentrações utilizadas e comparação em termos de acurácia e segurança com o padrão-ouro, que é o TPO [35].

Não existem dados bem definidos e agrupados na literatura mundial sobre testes cutâneos à fármacos em EPF, sendo necessárias revisões sistemáticas para validar a acurácia e a segurança dessa técnica diagnóstica.

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3. OBJETIVOS

3.1 Objetivo Geral

Investigar a acurácia e a segurança dos testes cutâneos de contato (*patch test* e/ou provocação tópica) como métodos substitutos ao teste de provocação oral na identificação do agente causador da farmacodermia em pacientes com eritema pigmentar fixo.

3.2 Objetivos Específicos

3.2.1 Comparar a acurácia diagnóstica combinada: estimar a sensibilidade e a especificidade dos testes cutâneos de contato (*patch test* e provocação tópica aberta) em comparação ao teste de provocação oral (padrão-ouro) em pacientes com EPF.

3.2.2 Analisar a positividade por classe farmacológica: determinar a prevalência de positividade nos testes de contato para diferentes classes de medicamentos, excipientes e metabólitos, identificando se determinados fármacos apresentam maior taxa de indução de resposta do que outros.

3.2.3 Avaliar a influência da topografia na sensibilidade: comparar as taxas de positividade entre testes realizados em pele previamente lesional e pele não lesional.

3.2.4 Analisar variáveis técnicas da testagem: verificar se a taxa de positividade varia significativamente conforme o veículo utilizado, a concentração do fármaco e o uso de substância pura em comparação ao produto comercial (com excipientes).

3.2.5 Avaliar o perfil de segurança e reatividade: avaliar o risco de reativação das lesões e a ocorrência de efeitos adversos locais ou sistêmicos, comparando o perfil de segurança entre o teste de provocação oral, o *patch test* e a provocação aberta (ROAT).

3.2.6 Determinar a janela temporal ideal para testagem: analisar a prevalência de positividade em função do intervalo decorrido entre o episódio agudo da farmacodermia e a realização dos testes.

3.2.7 Avaliar fatores do hospedeiro: investigar se variáveis individuais, faixa etária, estado imunológico e a presença de comorbidades, exercem influência na reatividade dos testes cutâneos.

3.2.8 Sintetizar evidências via meta-análise: construir a curva SROC (*Summary Receiver Operating Characteristic*) e calcular a sensibilidade combinada utilizando modelos Bayesianos bivariados, a fim de estabelecer o valor preditivo dos testes cutâneos como substitutos do teste de provocação oral.

4. ARTIGO REDIGIDO EM INGLÊS

“Diagnostic Accuracy and Safety of Epicutaneous Testing in Fixed Drug Eruption: Systematic Review and Metanalysis”

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ABSTRACT

INTRODUCTION: Fixed drug eruption (FDE) is a delayed drug reaction in which oral provocation testing (OPT) remains the diagnostic gold standard despite safety and ethical concerns. Skin tests, including patch test (PT) and the repeated open application test (ROAT), may be safer alternatives, but their diagnostic accuracy remains uncertain.

OBJECTIVES: To evaluate the diagnostic accuracy and safety of patch testing and ROAT, as complementary tools to OPT, for identifying the culprit drug in FDE.

METHODS: Systematic review and meta-analysis followed PRISMA-DTA/2020 guidelines and the PIRD framework. Five databases (MEDLINE, Embase, LILACS, Scopus, and Web of Science) were searched from 1972 to October 2025. Quality was assessed via QUADAS-2 for studies in quantitative synthesis. A bivariate Bayesian random-effects model estimated pooled sensitivity and specificity and generated the summary receiver operating characteristic (SROC) plot.

RESULTS: Seventy-eight studies were included in the qualitative synthesis, comprising 225 paired diagnostic interventions in 145 patients; 25 studies provided data for meta-analysis. Patch testing showed low pooled sensitivity (0.220; 95% CrI 0.060–0.441) and high specificity (0.964; 95% CrI 0.898–0.992), with positive and negative likelihood ratios of 5.98 and 0.81, respectively. Performance was higher on lesional than non-lesional skin (19.2% vs 5.0%; OR 7.05, 95% CI 2.03–24.39) and varied by drug class. Safety was favorable, with local reactivation in 2.9% of PT and one systemic reaction.

LIMITATIONS: Evidence was limited by small, mostly descriptive studies, scarce negative controls, absence of immunosuppressed patients in the accuracy dataset, and imprecise ROAT specificity estimates.

CONCLUSION: Patch testing and ROAT may aid FDE investigation, particularly when applied to lesional skin, but their low sensitivity limits their rule-out value. They should complement, not replace, OPT until standardized prospective evidence is available. Standardized prospective studies are needed.

Keywords: Fixed Drug Eruption; Drug Eruption; Patch Tests; Skin Tests; Oral Provocation Test; Systematic Review.

Introduction

Fixed Drug Eruption (FDE) is a cutaneous adverse drug reaction in which lesions recur at the same anatomical site upon re-exposure to the drug. [1-4] It is a T-cell-mediated delayed hypersensitivity reaction, with a localized inflammatory response dependent on CD8+ resident memory T cells (Trm). These cells persist at the dermo-epidermal junction of the affected areas and are rapidly reactivated following re-exposure. This characteristic explains both the local recurrence and the diagnostic difficulty, as the immune response is restricted to previously sensitized sites rather than being diffuse across the skin.[4,5]

Although its prevalence in the general population is low, FDE accounts for 7–21% of all drug eruptions.[2,5,6] Antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, anticonvulsants, and antimalarials are the most frequently implicated classes.[6-10] However, etiological identification is often hindered by polypharmacy and the lack of systematic confirmation, which limits the reliability of data in the literature.[11-16]

The oral provocation test (OPT) remains the gold standard for the etiological diagnosis of drug eruptions, but its application is limited by ethical and safety considerations regarding re-exposure to the culprit drug.[17-21] Lower-risk alternatives include skin tests (or epicutaneous tests or epicutaneous testing), such as the patch test (PT) and the Repeated Open Application Test (ROAT).[13,22] The American Academy of Allergy, Asthma, and Immunology (AAAAI) recognizes that patch testing may play a role in investigating delayed hypersensitivity drug reactions; however, due to its dependence on multiple technical factors and the scarcity of standardized protocols, its routine use is not recommended.[12,23-26]

The diagnostic performance of PT in FDE is influenced by multiple factors,[23,24,22] notably the application site, the interval following the acute episode, the vehicle, and the drug concentration. Testing on non-lesional skin, such as the back (the traditional PT site), may result in false negatives due to the localized distribution of resident memory T cells.[11,12,22,23,24,27,28] Additionally, the lack of vehicle standardization and sensitization to metabolites or excipients, which are often not tested, may interfere with skin reactivity,[5,11,12,22,27,28] as these elements, rather than the drug itself, may be the actual causative agents of the reaction.[5]

These variables justify the wide oscillation in positivity rates reported in the literature, which reach 40–87% in FDE.[12] The shortage of studies systematically correlating skin tests with the gold standard, OPT, limits the true assessment of their accuracy.[11-15] Furthermore, FDE frequently affects areas difficult to occlude, such as oral and genital mucosae. In these cases, ROAT has been proposed, in which the medication is applied directly over the previously affected site.[28-31] Studies have shown that this method can identify early reactions not detected during conventional PT readings,[29,30] and recent recommendations have established standardized protocols for its use in FDE diagnosis.[31]

Despite these alternatives, there remains a lack of robust data systematically comparing PT and ROAT to OPT, as well as a lack of information regarding the technical factors and safety of these procedures. The absence of a precise etiological diagnosis can lead to significant morbidity, resulting in the unnecessary discontinuation of drugs or the use of less effective alternative therapies.

Given these gaps, the present study aimed to conduct a systematic review and meta-analysis to evaluate the diagnostic accuracy and safety of skin tests used in FDE, as well as to investigate technical factors associated with the performance of these methods compared to OPT.

Methods

This systematic review and meta-analysis of diagnostic test accuracy was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses of Diagnostic Test Accuracy (PRISMA-DTA) and the PRISMA 2020 statements.[32,33] The study followed a pre-specified protocol prospectively registered on the PROSPERO platform (CRD42024486891).

Eligibility Criteria

Eligibility criteria followed the PIRD framework (Population, Index test, Reference standard, Target Diagnosis) for diagnostic test accuracy reviews.[34,35] We included studies of any design involving pediatric or adult patients with clinical or histopathological diagnosis of FDE, regardless of variant, lesion extent, or immunological status. Index tests were PT and/or ROAT on lesional or non-lesional skin, when sufficiently described for data extraction. The reference standard was OPT with the same drug, in the same patient; studies using subcutaneous or intravenous provocation were excluded. Inclusion required paired index-test and reference-standard data for the same patient and drug, with culprit-drug identification as the target diagnosis.

Studies were eligible regardless of design (single case reports, case series, retrospective record reviews, prospective studies), provided that paired data

from the index test and the reference standard were reported for the same patient and the same drug.

Exclusion Criteria

Exclusion criteria were publications prior to 1972; reviews, editorials, letters, and conference abstracts without complete data; studies addressing other drug eruptions without paired FDE data; exclusively *in vitro* studies; studies without OPT as the comparator; and reports that did not identify the tested drugs or their respective outcomes. The 1972 lower date limit was prespecified in the PROSPERO protocol (CRD42024486891), and its potential impact is addressed in the Discussion.

Search Sources

Searches were performed in MEDLINE via PubMed, Embase, LILACS, Scopus, and Web of Science on October 21, 2025. For each database, a specific search strategy was adapted according to its indexing terms, syntax, and available search fields. The strategy included controlled vocabulary terms, when available, and free-text terms related to FDE, patch testing/skin testing, and oral provocation/drug administration. Synonyms within each concept were combined using the Boolean operator OR, and the three main concepts were combined using AND. The complete search strategies for all databases are available in Supplementary File 1. The final PubMed search strategy was as follows:

("Fixed drug eruption"[tw] OR "Fixed pigmented erythema"[tw])

AND

("Skin Tests"[Mesh] OR "Patch Tests"[Mesh] OR "Patch Tests"[tw] OR "Patch Test"[tw] OR "Patch, Tests"[tw] OR "Testing, Patch"[tw] OR "Topical provocation"[tw])

AND

("Oral provocation"[tw] OR "Administration, Oral"[Mesh] OR "Drug Administration oral"[tw] OR "Oral Drug Administration"[tw] OR "Oral Administration"[tw] OR "Oral Administrations"[tw] OR "Oral Drug"[tw] OR "Drug Administrations"[tw] OR "Oral Drug Administrations"[tw] OR "Drug Provocation Test"[tw] OR "Provocation Tests"[tw]).

Study Selection

Two reviewers (FBO and AC) independently screened titles and abstracts based on predefined eligibility criteria. Records that did not meet the inclusion criteria or met any exclusion criteria were excluded. The remaining records, as well as those with insufficient information in the abstract to allow exclusion, were retrieved for full-text assessment. Full-text articles were then independently evaluated by the same reviewers to determine final eligibility. Any disagreements were resolved by consultation with a third reviewer (RRB).

Data Extraction

Data extraction followed a standardized and independent protocol, with records organized in an electronic spreadsheet (Microsoft Excel®), and discrepancies resolved by consensus between the reviewers. Diagnostic accuracy parameters were collected, including sensitivity, specificity, positive and negative predictive

values, and concordance with the OPT, as well as safety indicators, such as the occurrence of adverse reactions and lesion reactivation.

The extraction also covered methodological characteristics of the tests, including the type of test and application site, vehicle, drug concentration, reading time, and the interval elapsed after the drug eruption. Finally, clinical characteristics of the patients were recorded, including the clinical presentation of the lesion, age group, presence of comorbidities, and immunological status.

Quality Assessment (Risk of Bias)

Risk of bias was assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool for studies providing sufficient study-level data for the diagnostic accuracy meta-analysis. [36] Studies lacking the minimum structural requirements for QUADAS-2 assessment, such as negative controls, defined patient flow, or consistently applied reference standards, were not evaluated with this tool; this restriction is addressed in the Discussion. Two reviewers (FBO and AC) independently assessed the four QUADAS-2 domains (patient selection, index test, reference standard, and flow and timing) with disagreements resolved by consensus or by a third reviewer (RRB). Domains were rated as low, high, or unclear risk of bias. Studies with high risk in any technical domain were classified as high overall risk, while those with concerns restricted to patient selection were classified as having some concerns.

Outcomes and Variables

Primary outcomes included diagnostic accuracy (sensitivity, specificity, and concordance with the gold standard) and safety (local and systemic reactions,

new lesions, and lesion reactivation). The influence of test characteristics, including application type (closed or open), application site (lesional or non-lesional skin), vehicle, drug concentration, reading time, and the interval between the drug eruption and test performance, was investigated. Clinical and demographic variables, such as lesion presentation (bullous or non-bullous), age group, presence of comorbidities, and immunological status, were also analyzed.

Statistical Analysis

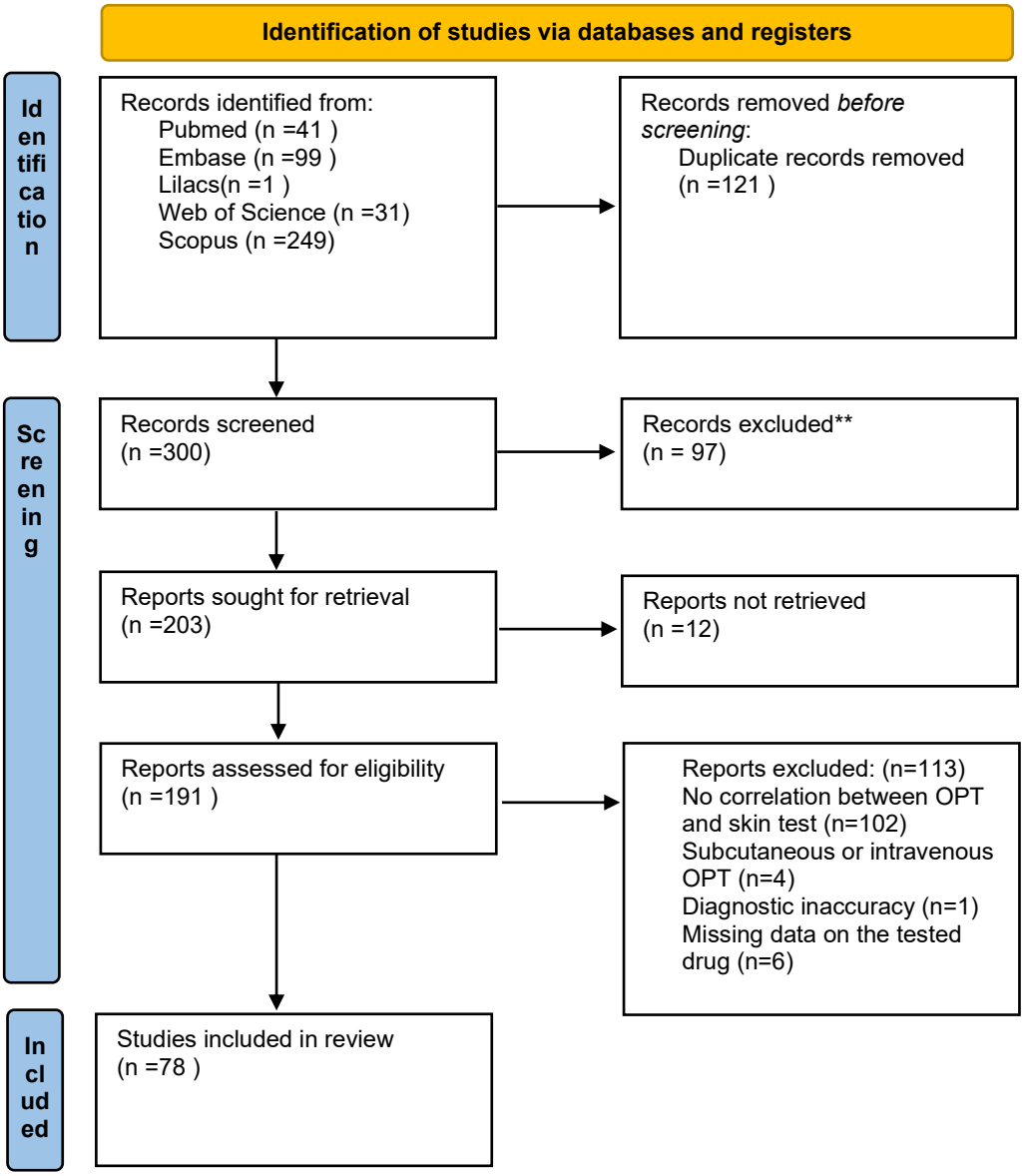
Sample characterization and safety profiles were performed through descriptive analysis (absolute and relative frequencies). Associations between categorical variables and drug classes were evaluated using the Breslow-Day, Cochran, and Mantel-Haenszel (Odds Ratio estimation) tests, and Fisher's Exact Test (or the Freeman-Halton extension for tables larger than 2x2). Homogeneity between strata was verified by the Breslow-Day test. The significance level was set at 5% ($p < 0.05$), utilizing IBM SPSS v.24 software.

Quantitative Synthesis (Meta-analysis)

The accuracy meta-analysis utilized a bivariate Bayesian random-effects model via the MetaBayesDTA platform.To estimate pooled sensitivity and specificity, derive likelihood ratios and the diagnostic odds ratio, and generate the summary receiver operating characteristic (SROC) plot with its 95% credibility region and 95% prediction region data were aggregated by study to mitigate multiple-unit bias. In parallel, subgroup analyses were calculated based on individual tests to evaluate drug-specific specificities.

Results

Search Results and Study Characteristics



*All records were excluded by a human

**All records were excluded by a human

Figure 1: PRISMA flow diagram of the systematic review

The initial search yielded 421 articles (Figure 1). After removing 121 duplicates, 300 titles and abstracts were screened, leading to the exclusion of 97 studies. Of the 203 articles selected for full-text analysis, 125 were excluded for the following reasons: 102 for failing to correlate oral provocation with skin testing; 12 due to the impossibility of accessing the full text; 4 for using subcutaneous or intravenous provocation routes; 1 for inaccuracy in the etiological diagnosis; and the remaining 6 for a lack of specific data regarding the tested drug in aggregated samples. Ultimately, 78 articles met the criteria and were included in the review, consisting of 66 single case reports, 7 case series, 2 retrospective studies based on medical record reviews, and 3 prospective studies (Supplementary Table 1). The number of cases included per study ranged from 1 to 27, with a mean of 1.86 and a standard deviation of 3.95.

Sample Characteristics

Overall, the studies culminated in 310 tests; however, the specific sample of oral provocation associated with skin testing totaled 225 tests in 145 different patients. For the accuracy analysis, the studies were disaggregated into cases and tests, including only patients who underwent both the OPT and the skin test with the same medication. The entire sample consisted of non-immunosuppressed individuals. Regarding FDE variants, the non-bullous form was observed in 91.0% (n = 132), bullous in 6.9% (n = 10), and mixed in 2.1% (n = 3). The extent of the lesions was classified as up to 5 lesions in 57.2% (n = 83), single in 40.7% (n = 59), and generalized in 2.1% (n = 3). The mean age was 38.79 years (SD 18.85) among 131 patients (for whom this information was

reported), with 51.9% (n = 69) being female in 133 records. The majority (88.3%) had no comorbidities.

The analysis of 310 skin tests revealed a predominance of NSAIDs/Analgesics (29.4%) and antibiotics (26.8%), which together account for more than half of the sample. Among antibiotics, sulfonamides represented the most frequent subgroup (11.9% of the overall sample).

Other categories with significant representation included the group composed of allopurinol and vitamins (14.8%), in addition to excipients (6.8%) and antihistamines (6.5%). Other pharmacological classes, such as anticonvulsants, antifungals, and antivirals, presented individual frequencies below 6%.

The vast majority of the tested drugs, 73.5% (n = 228), were the suspected culprit of the drug reaction, while 26.5% (n = 82) were tested as alternative drugs to evaluate new therapeutic possibilities or cross-reactivity. The classes of tested medications are detailed in Table 1.

Table 1. Frequency and Distribution of Drug Classes Tested in the Sample (n = 310)

Pharmacological Class	Main Subgroup	Frequency (n)	Percentage (%)
NSAIDs / Analgesics	–	91	29.4%
	Propionic/Acetic Acid Derivatives	35	11.3%
	Other NSAIDs	22	7.1%
	Paracetamol	11	3.5%
	Pyrazolones	9	2.9%
	Salicylates	8	2.6%
	Fenamates	4	1.3%
	Coxibs	2	0.6%
Antibiotics	–	83	26.8%
	Sulfonamides	37	11.9%
	Quinolones	12	3.9%
	Penicillins	11	3.5%
	Other classes	23	7.4%
Others (Allopurinol/Vitamins)	–	46	14.8%
Excipients	–	21	6.8%
Antihistamines	–	20	6.5%
Anticonvulsants	–	16	5.2%
Antifungals	–	12	3.9%
Other classes*	–	21	6.6%
Total	–	**310**	**100.0%**

Legend:
n = number of tests performed.
NSAIDs = non-steroidal anti-inflammatory drugs.
*Includes antivirals, antiparasitics, herbal medicines, and cardiovascular drugs.

Positivity and Accuracy of Diagnostic Tests

The positivity of skin tests (PT and topical provocation) and oral tests underwent a multifactorial evaluation to identify variables influencing diagnostic reactivity. The analysis was stratified by clinical and methodological parameters, including the testing site, the time interval between the drug eruption manifestation and test execution, reading time, and the vehicle used. Additionally, the influence of the drug, metabolites, and excipients on the accuracy of the etiological diagnosis was assessed. PT results were analyzed considering both the intrinsic efficacy of the application site and the distribution of positivity across the total sample of 310 tests. The overall positivity rate for all tests performed was 15.5% (48/310).

Regarding PT positivity in relation to clinical suspicion, a statistically significant association was observed between the drug being the primary suspect of the reaction and the test result ($p = 0.0001$). Among medications that constituted the primary suspicion because they were used by the patient at the time of the reaction ($n = 222$), the PT positivity rate was 19.8% ($n = 44$). Conversely, when drugs were tested only as therapeutic alternatives without direct suspicion ($n = 84$), positivity was significantly lower, occurring in only 3.6% ($n = 3$) of the cases.

The analysis of PT performance in FDE demonstrated a clear dependence on the application site (Table 2). Overall positivity was 15.6%, with a significant difference between lesional skin (19.2%) and non-lesional skin (5.0%) ($p <$

0.001). The odds ratio was 7.05 (95% CI: 2.03–24.39), indicating an approximately seven-fold higher probability of diagnostic confirmation when the drug was applied over the residual macule compared to healthy skin.

Overall specificity was 94.9%, reaching 100% when the test was performed directly on the lesion, with no false positives occurring. Overall sensitivity was 24.8%, being slightly higher when testing was performed simultaneously at both lesional and non-lesional sites. (28.6%). The analysis demonstrated consistency of results across studies (p = 0.799)Table 2 presents the positivity and sensitivity data according to the application site, considering both the total samples and the subgroup subjected to the OPT.

Table 2. Diagnostic Accuracy of Patch Testing in Fixed Drug Eruption According to Application Site

Test Site	Positivity (n = 307)	Sensitivity (n = 224)	Specificity (n = 224)
Lesional skin	19.2% (10/52)	20.6%	100.0%
Non-lesional skin	5.0% (4/80)	15.4%	100.0%
Both	19.4% (34/175)	28.6%	93.6%
Overall	15.6% (48/307)	24.8%	94.9%

Legend:
n = number of tests.
Positivity calculated based on the total number of tests performed.
Sensitivity and specificity validated using oral drug provocation testing.
Association statistics: Cochran test (Q = 11.87; p < 0.001); Mantel–Haenszel common odds ratio = 7.046 (95% CI: 2.035–24.393); Breslow–Day test for homogeneity (p = 0.799)

In a specific analysis of the 41 open topical provocation interventions performed, a positivity rate of 85.4% (n = 35) was observed on lesional skin, with positivity occurring simultaneously on both lesional and non-lesional skin in only 0.2% (n = 1) of cases. Regarding negative results, these were found in 1.6% of the sample, subdivided into 0.3% (n = 1) showing negativity at both sites and 1.3% (n = 4) with negativity restricted to the tested area.

The positivity of the PT also varied significantly according to the drug class tested ($p < 0.001$). The diagnostic performance, stratified by pharmacological class and validated by accuracy indicators, is presented in Table 3. Anticonvulsants showed 68.8%, confirming the high diagnostic value for this group, while NSAIDs (13.2%) and antibiotics (9.6%) had low positivity rates. In addition to the positivity rate, sensitivity, specificity, and positive and negative predictive values were calculated for cases subjected to both PT and OPT.

Table 3. Diagnostic Performance of Patch Testing Stratified by Pharmacological Class

Analysis Group	n (Valid)	Sensitivity	Specificity	PPV	NPV
All drugs	224	24.8%	94.9%	93.2%	31.1%
Anticonvulsants	16	78.6%	100%	100%	40.0%
Antihistamines	11	66.7%	100%	100%	71.4%
Others (Allopurinol/Vitamins/Mucolytics)	35	42.1%	87.5%	80.0%	56.0%
NSAIDs / Analgesics	52	21.2%	94.7%	87.5%	40.9%
Excipients	10	20.0%	100%	100%	55.6%
Antibiotics	75	12.1%	100%	100%	13.4%
Antifungals	8	0.0%	100%	–	25.0%
Antivirals	4	0.0%	100%	–	25.0%

Legend:
n (Valid) = tests with available results for both patch test and oral provocation.
PPV = positive predictive value.
NPV = negative predictive value.
$p < 0.001$ for sensitivity variation across drug classes.

Regarding the association between the nature of the tested drug and PT positivity in a sample of 307 cases, a significant variation in results was observed ($p = 0.0006$). Drugs classified as metabolites (for example, thiodiglycolic acid, which is a metabolite of carbocisteine) showed the highest positivity rate, with 100% of cases ($n = 7$) demonstrating a positive reaction. Furthermore, a significant association was observed between the nature of the tested substance and PT positivity ($p = 0.025$). The positivity rate was higher among excipients (57.9%; 11/19) than among drugs not classified as excipients

(31.9%; 92/288). Likewise, a significant association was observed between the vehicle used and test positivity ($p < 0.001$; $\chi^2 = 43.799$; $df = 10$).

Among the 310 PT analyzed, petrolatum was the most frequently used vehicle (74.5%), with a positivity rate of 12.1%, while DMSO, although used in only 5 cases, showed 100% positivity (Table 4).

Table 4. Influence of Vehicles on Patch Test Positivity

Vehicle	Total n	Positive (n)	Negative (n)	Positivity (%)
Petrolatum	231	28	203	12.1%
Not reported	39	11	28	28.2%
Petrolatum / DMSO	14	2	12	14.3%
No vehicle	11	0	11	0.0%
DMSO alone	5	5	0	100.0%
Aqueous / solution	3	2	1	66.7%
Other*	4	0	4	0.0%
Total	**307**	**48**	**259**	**15.6%**

Legend:
n = number of tests performed.
DMSO = dimethyl sulfoxide.
*Includes alcohol, cream, powder/tablet, and ointment

In the open provocation test, petrolatum was the most frequently used vehicle (n = 38), with a positivity rate of 92.1% (35/38). In the comparative group (no vehicle or others), positivity was 33.3% (1/3), a difference that proved to be statistically significant ($p = 0.035$).

The analysis of the concentrations used in the skin tests revealed wide methodological heterogeneity among the studies. The 0.1% concentration was the most frequent, used in isolation in 29.4% of the tests (91/310). Protocols with progressive series were also utilized, notably the 10%, 20%, and 50% concentrations (12.3%; 38/310), followed by 1% and 10% (3.9%; 12/310) and the combination of 0.1%, 1%, and 10% (2.6%; 8/310).

Other concentrations showed lower frequencies, such as 0.01% (4.8%; 15/310) and 0.05% (4.2%; 13/310), while specific doses used for penicillins (e.g.,

250,000 IU/mL) represented only 1% of the sample (3/310). In 11.6% of the cases (36/310), the concentration was not described, highlighting a lack of standardization in the literature regarding the doses used in skin tests.

The analysis of diagnostic performance according to reading protocols demonstrated that the intermediate interval (48–96h) provided the largest volume of evaluable data, representing 79.6% of the analyzed readings (n = 129). In this group, sensitivity was 20.2% and specificity was 96.7%. Early readings (≤ 24h) and late readings (> 96h) accounted for 12.3% (n = 20) and 8.0% (n = 13) of the evaluable interventions, respectively. These results confirm that while early readings can capture rapid reactivations with superior sensitivity and specificity, despite a smaller sample size ,the intermediate interval (48–96h) remains the standard supported by the most robust volume of data in FDE.

Regarding the interval between the acute episode and the performance of the test, a time window of higher reactivity was observed. Testing performed within two weeks showed the best performance, with a sensitivity of 45.0%, specificity of 94.7%, and an odds ratio of 14.72 (95% CI: 1.78–121.2). Longer intervals showed a progressive reduction in sensitivity, reaching 2.0% in the 3–6 week period (OR = 0.06; 95% CI: 0.006–0.71), a trend that was maintained in subsequent intervals. The temporal heterogeneity was significant ($p < 0.001$). The group without chronological information (n = 84) showed a sensitivity of 35.1%, suggesting that the absence of this data in primary studies may hide periods of higher reactivity. These data are compiled in Table 5.

Table 5. Diagnostic Accuracy of Patch Testing: Reading Protocols and Time Intervals (n = 224)

Variable and Category	n (Valid)	Sensitivity	Specificity	Odds Ratio (95% CI)
Reading Time				
Early (≤24 h)	20	47.1%	100.0%	–
Intermediate (48–96 h)	129	20.2%	96.7%	–
Late (>96 h)	13	16.7%	100.0%	–
Interval after FDE				
≤2 weeks	59	45.0%	94.7%	14.72 (1.78–121.2)
3–6 weeks	53	2.0%	75.0%	0.06 (0.006–0.71)
7–12 weeks	7	25.0%	66.7%	0.66 (0.02–20.4)
>3 months	21	6.7%	100.0%	0.00
Not reported	84	35.1%	100.0%	10.81 (1.00–116.4)

Legend:
n = number of cases confirmed by oral drug provocation testing.
95% CI = 95% confidence interval.
Odds ratios calculated using the Mantel–Haenszel method.

Regarding the interval between the acute episode and the performance of the OPT (n = 226), a high proportion of unreported data was observed (61.5%; n = 139). Among the documented cases, the most frequent intervals were 2-3 weeks (11.9%; n = 27) and 4-5 weeks (8.8%; n = 20). Intervals of 8-12 weeks represented 4.4% of the sample (n = 10), while periods of 7 months to 1 year and over 1 year corresponded to 4.0% each (n = 9). Other intervals were less frequent, including 6-7 weeks (3.1%; n = 7), 1 week (0.3%), 12-16 weeks (0.6%), and 4-6 months (0.6%). Despite the high proportion of missing data, the available records indicate that diagnostic investigation occurred predominantly between 1 and 5 weeks after the resolution of the acute episode.

Diagnostic Performance Meta-analysis

The diagnostic performance of the PT in FDE was evaluated from two complementary perspectives. In the patient-level analysis (n = 143), considering the paired protocol, 41 true-positive, 96 false-negative, 3 false-positive, and 3 true-negative results were observed. In this analysis, the sensitivity was 29.93%

and the positive predictive value (PPV) reached 93.18%, indicating high diagnostic reliability when the result is positive.

When expanding the analysis to the diagnostic intervention level (n = 225), accounting for each drug independently, the test showed 41 true-positives, 56 true-negatives, 3 false-positives, and 125 false-negatives. The overall accuracy was 43.11% (97 correct results out of 225 tests), with a specificity of 94.92% and sensitivity of 24.85%. The PPV remained at 93.18%, while the negative predictive value (NPV) was 31.11%.

The presence of 181 negative results in this analysis represents the potential of the test to yield negative outcomes; however, the high number of false-negatives (55.56% of interventions) confirms that a negative result is not sufficient to rule out clinical suspicion, thus maintaining the OPT as the gold standard for the definitive exclusion of drug causality.

Patient-level specificity (50.0%) and NPV (3.0%) for patch testing should be interpreted with caution, because they are based on only six paired negative-control observations and carry very wide uncertainty intervals. The intervention-level estimates (specificity 94.9%; NPV 31.1%), calculated over 225 paired interventions, are statistically more stable and were used as the primary reference for the Bayesian meta-analysis.

At the OPT (n = 225), the overall positivity rate was 71.6%. Antibiotics were confirmed in 88% of cases and anticonvulsants in 87.5%. The comparison between the PT and the gold standard showed an overall sensitivity of 29.93% and a PPV of 93.18%, with 96 false-negative results.

For open provocation (n = 41), the diagnostic performance was superior to that of the PT, with concordance in 37 cases (35 true-positives and 2 true-

negatives). The sensitivity was 92.1% (35/38) and the specificity was 100% (2/2), with only 3 false-negatives. Positivity occurred predominantly on lesional skin, present in 85.4% of interventions (n = 35), with only one case of simultaneous positivity on lesional and non-lesional skin (0.3%). The 100% specificity should be interpreted with caution due to the small number of negative controls in this sub-analysis. The results are summarized in Table 6.

Table 6. Diagnostic Performance of Patch Testing and Open Drug Provocation in Fixed Drug Eruption

Unit of Analysis	n	Sensitivity	Specificity	PPV	NPV	Accuracy
Patch Test (Patient)	143	29.93%	50.00%*	93.18%	3.03%*	30.77%
Patch Test (Intervention)	225	24.85%	94.92%	93.18%	31.11%	43.30%
Open Provocation	41	92.10%	100.00%	100.00%	40.00%	90.24%

Legend:
n = number of patients or interventions.
PPV = positive predictive value.
NPV = negative predictive value.
*Patient-level specificity and negative predictive value (NPV) for patch testing were calculated based on only six paired negative-control observations and should therefore be interpreted as unstable descriptive estimates with very wide confidence intervals, rather than as robust measures of diagnostic performance. Patient-level sensitivity is reported on a larger denominator (143 patients) and is less affected by this limitation.

Meta-analysis

Although 78 studies were included in the qualitative systematic review, only 25 provided sufficient study-level data to construct 2×2 diagnostic accuracy tables and were therefore eligible for the quantitative meta-analysis. The remaining 53 studies ,predominantly single case reports without negative controls, or with exclusive reporting of positive outcomes, could not contribute to pooled estimates of sensitivity and specificity, since these parameters require both true-positive/false-negative and false-positive/true-negative cells at the study level. All the studies are described in Supplementary Table 2. The figures and pooled estimates presented below therefore refer to the 25 studies included in

the quantitative synthesis, and not to the entire body of evidence retrieved by the systematic review. The bivariate Bayesian meta-analysis estimated an overall PT sensitivity of 22% (95% CrI: 6–44%) and a specificity of 96.4% (95% CrI: 89.8–99.2%) compared to oral provocation.

The summary receiver operating characteristic (SROC) plot derived from the bivariate Bayesian random-effects model is presented in Figure 2.

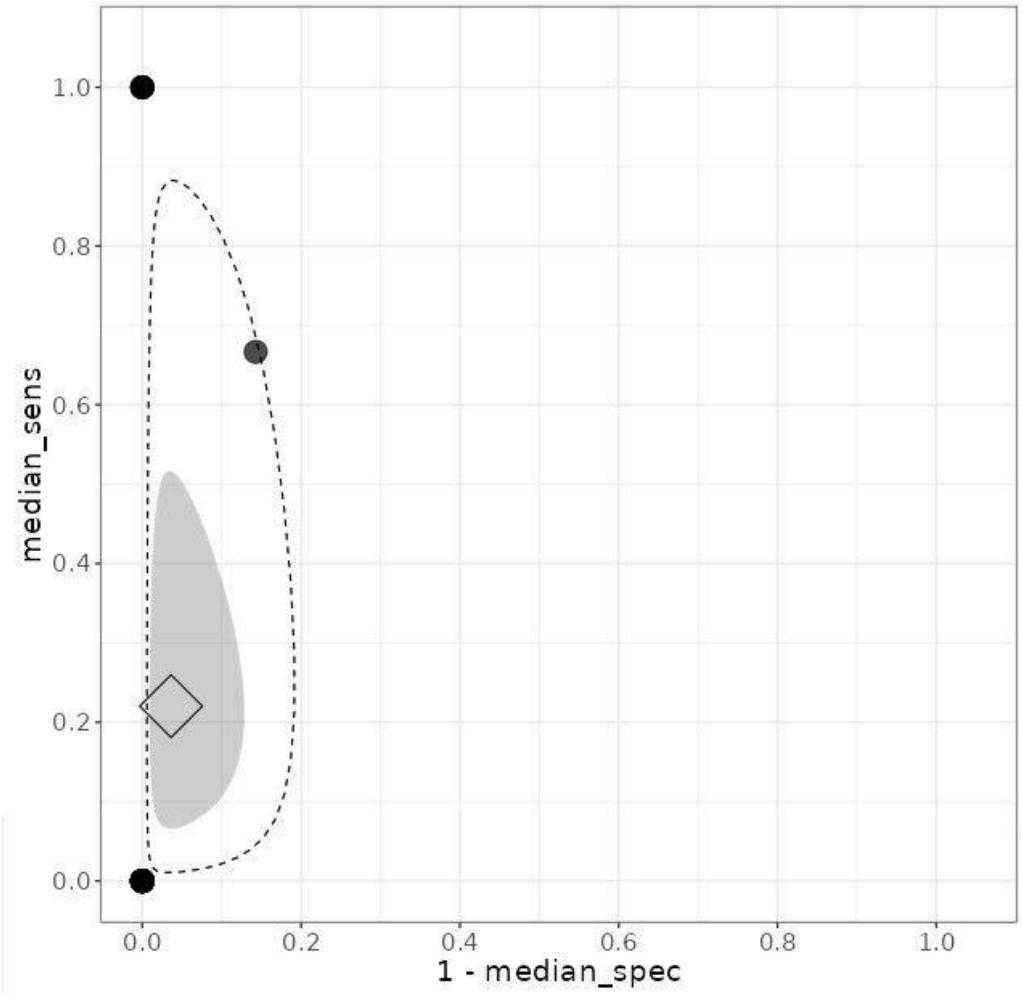


Figure 2: Summary Receiver Operating Characteristic (SROC) curve of skin testing performance in Fixed Drug Eruption.

Legend: Summary receiver operating characteristic (SROC) plot for patch testing in fixed drug eruption, derived from the bivariate Bayesian random-effects model based on the 25 studies included in the quantitative diagnostic accuracy meta-analysis. The x-axis represents the false-positive rate (1 − specificity) and the y-axis represents sensitivity. Individual study estimates are plotted as solid points. The open diamond indicates the summary point (median posterior sensitivity 0.220 [95% CrI 0.060–0.441]; median posterior specificity 0.964 [95% CrI 0.898–0.992]). The shaded area represents the 95% credibility region for the summary point, reflecting uncertainty around the pooled estimate. The dashed contour represents the 95% prediction region, indicating the expected range of true sensitivity and specificity for a future study drawn from the same underlying distribution.

Wide variability was observed among the studies regarding the sensitivity estimate, with several publications showing null values and few demonstrating high performance, indicating relevant heterogeneity. In contrast, specificity remained consistently high, with point estimates near 1.00 in most studies, albeit with wide credibility intervals due to the small sample sizes. The false-positive rate was low (3.6%), while the false-negative rate remained high. The representative graphs of the meta-analysis are presented below in Figures 3 and 4.

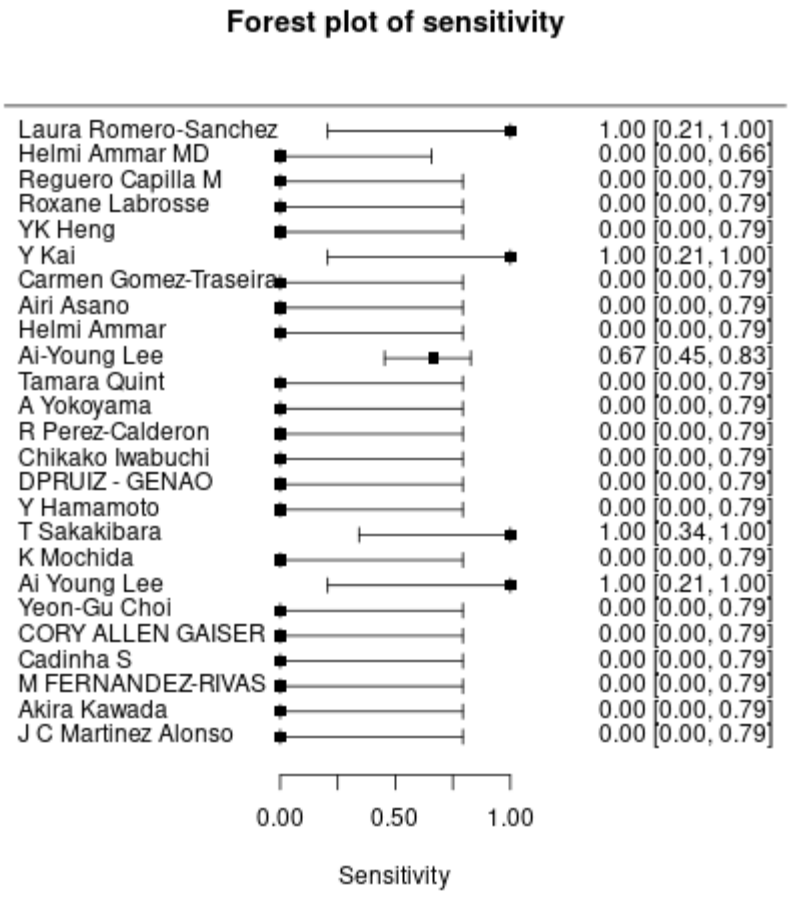


Figure 3. Forest plot of sensitivity for the 25 studies included in the meta-analysis.

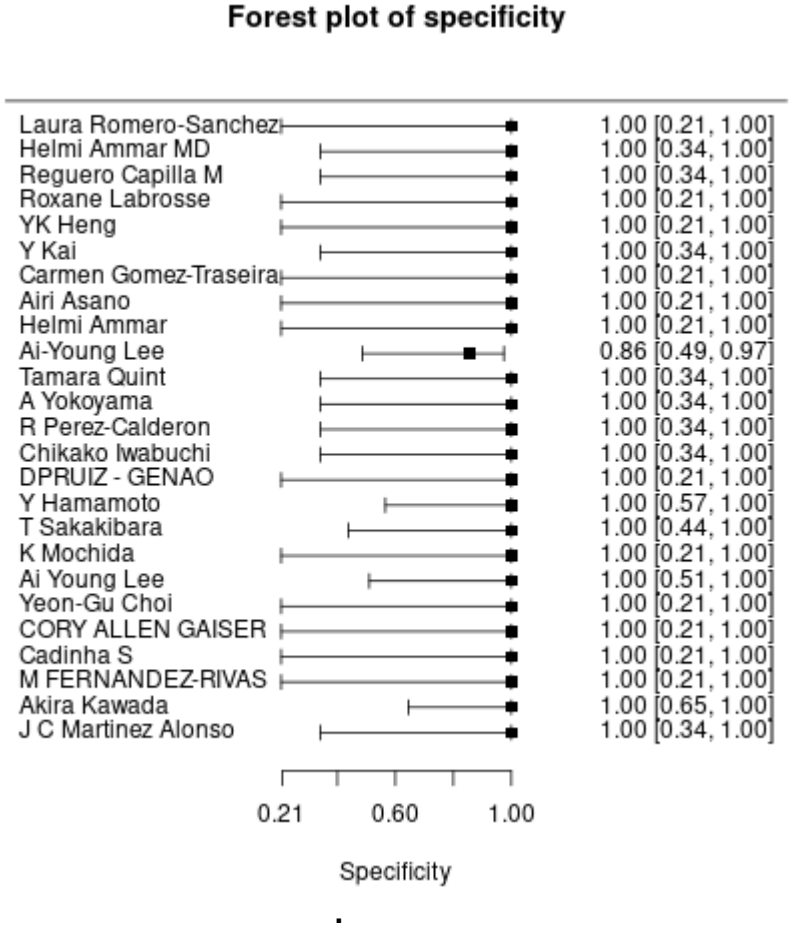


Figure 4. Forest plot of specificity for the 25 studies included in the meta-analysis

Safety of Diagnostic Tests

Regarding safety, 96.7% of the PT (297/307) showed no adverse effects beyond the expected local erythema associated with positivity. Local reactivation occurred in 3% (9/307) and systemic symptoms (fever) in 0.3% (1/307). In the analysis by drug class, antibiotics (n = 51) and anticonvulsants (n = 5) showed no adverse reactions. Among NSAIDs (n = 34), 30 patients had no complications, while 4 experienced local reactivation. In the group of other

medications (n = 217), 211 showed no reactions, 5 showed local reactivation, and the only case of local reactivation associated with fever was recorded.

In the OPT (n = 222), local reactivation was the most frequent outcome, occurring in 57.7% of cases (n = 128), followed by the absence of symptoms beyond test positivity in 38.3% (n = 85). More significant reactions, such as the appearance of new lesions and local reactivation associated with fever, occurred in 3.6% (n = 8) and 0.5% (n = 1), respectively. Local reactivation predominated among antibiotics (42/48), contrasting with the absence of reactions in the majority of NSAIDs (9/17) and in all anticonvulsants (n = 5). In the group of other medications (n = 152), outcomes were mostly divided between local reactivation (n = 78) and the absence of complications (n = 66), with rare reports of new lesions (n = 7) or fever (n = 1).

In open provocation (n = 30), the most common manifestation was redness and erythema, observed in 66.7% of patients (n = 20). The absence of additional symptoms and the presence of redness, erythema, and induration occurred in 16.7% of cases each (n = 5). No episodes of local reactivation or the appearance of new lesions were recorded. Antibiotics (n = 27) accounted for the majority of reactions, with 20 cases of redness and erythema and 5 of redness, erythema, and induration, while the group of other medications (n = 3) showed no adverse reactions. Table 7 displays the adverse effects and safety profile by diagnostic method and drug class.

Table 7. Safety Profile and Adverse Events of Diagnostic Methods in Fixed Drug Eruption

Test Modality	Pharmacological Class	No adverse events beyond test positivity	Local reactivation	Other reactions
Patch Test (n = 307)	Antibiotics	51	0	0
	NSAIDs	30	4	0
	Anticonvulsants	5	0	0
	Others	211	5	1 (fever)
Total		**297 (96.7%)**	**9 (3%)**	**1 (0.3%)**
Oral Provocation (n = 222)	Antibiotics	5	42	1 (new lesions)
	NSAIDs	9	8	0
	Anticonvulsants	5	0	0
	Others	66	78	8 (new lesions / fever)
Total		**85 (38.3%)**	**128 (57.7%)**	**9 (4.1%)**
Open Provocation (n = 30)	Antibiotics	0	0	25 (erythema / induration)
	Others	5	0	0
Total		**5 (16.7%)**	**0**	**25 (83.3%)**

Legend:
n = number of diagnostic interventions.

Quality Assessment of the Studies

The patient selection domain presented a high risk of bias in the majority of the studies, resulting from the predominance of case reports and clinical series that did not describe the consecutive inclusion of participants. In contrast, the index test and reference standard domains were mostly classified as low risk, with occasional concerns regarding the detailing of the PT's technical parameters. The flow and timing domain also presented a predominantly low risk.

For the overall judgment, studies with a high risk in the technical domains (index test, reference standard, or flow and timing) were categorized as having a high overall risk due to the direct impact on accuracy estimates. Conversely, those with limitations restricted to patient selection were classified as having "some concerns." Based on these criteria, 6 studies were defined as having a high

overall risk and 19 as having "some concerns," as detailed in the quality assessment chart (Figure 5).

Figure 5. Quality of the studies included in the meta-analysis according to the QUADAS-2 tool.

Discussion

This systematic review included 78 studies, of which 25 provided sufficient data for the meta-analysis. The evidence base predominantly comprises single case reports (66/78; mean 1.86 cases), highlighting the scarcity of robust samples in

FDE literature. This architecture conditions the interpretation of accuracy estimates, as it relies on small clinical series and heterogeneous methodologies. Notably, the tendency to perform the gold-standard OPT primarily after negative skin tests (selective verification), coupled with the publication bias favoring informative positive results, suggests that the observed high specificity may be inflated.

Single case reports typically showcase positive PT followed by confirmatory provocation. Conversely, drugs tested as therapeutic alternatives or cross-reactivity controls (26.5% of the sample) are usually skin-test negative and confirmed as tolerated, contributing true-negative cells to the diagnostic 2×2 table. This pattern enriches the dataset with true positives and selected true negatives, yielding specificity estimates potentially higher than those in consecutive clinical cohorts, while sensitivity remains strongly dependent on which culprit-drug confirmations were reported. Consequently, this over-representation of positive outcomes affects both the magnitude and stability of the parameters estimated by the bivariate Bayesian model.

The between-study heterogeneity parameters are themselves informative: the standard deviation for sensitivity ($\sigma_1 = 1.329$) was substantially larger than for specificity ($\sigma_0 = 0.430$). This is consistent with clinical observations that sensitivity is highly dependent on technical variables, such as vehicle, concentration, site, and timing, while specificity is more stable, as identifying drug tolerance is simpler than reactivating a hypersensitivity response in a previously sensitized site. The wide credibility interval for sensitivity (0.060–0.441) versus the narrow interval for specificity (0.898–0.992) reflects this asymmetry. Thus, the high stability of specificity across studies should not be

confused with high precision of the parameter in clinical populations not represented in this literature.

The analysis of 310 tests revealed an overall positivity rate of 15.5%. In tests paired with oral provocation (n = 225), sensitivity was 24.85% and specificity was 94.92%. In the patient-level analysis (n = 143), sensitivity was 29.93%, with a PPV of 93.18%. The Bayesian meta-analysis confirmed this trend, estimating an overall sensitivity of 22% (95% CrI: 6–44%) and a specificity of 96.4% (95% CrI: 89.8–99.2%). The positive likelihood ratio of 5.98 and the negative likelihood ratio of 0.81 reinforce that the test is effective for confirming, but insufficient for excluding, the diagnosis. Significant heterogeneity in sensitivity was observed across studies ($\sigma 1 = 1.33$), while the variability in specificity was lower ($\sigma 0 = 0.43$).

The observed sensitivity was lower than the rates of 31.5% to 87% previously reported in different populations.[7-11,13-16] This disparity may be attributed to methodological differences: in this review, the accuracy analysis required mandatory pairing between PT and OPT, a procedure that, in clinical practice, is often reserved only for cases with negative skin tests. Additionally, the sample included not only the suspected culprit drugs (73.5%) but also alternative medications tested for cross-reactivity or therapeutic options (26.5%), a factor that tends to reduce the overall positivity rate as mentioned before.

Stratified analysis revealed relevant variations in diagnostic performance. Anticonvulsants and antihistamines showed the best performance (sensitivity of 78.6% and 66.7%, respectively; specificity of 100%), while antibiotics showed significantly lower sensitivity (12.1%). NSAIDs and analgesics had intermediate performance (21.2%), whereas antifungals and antivirals showed null

sensitivity. This variation corroborates Barbaud and Romano's observations[11] regarding the greater utility of PT for non-injectable drugs and reinforces the hypothesis by Phillips et al.[28] that reactivity to antibiotics may depend on systemic metabolites not reproduced in topical application.

In this context, the low testing rate for metabolites and excipients (6.8%) may have increased false-negative rates. The 100% positivity observed with metabolites supports the propositions of Shiohara et al. and Barbaud et al.,[5,37] as well as the pro-hapten concept by Demoly et al.,[2] suggesting that certain drugs require metabolic conversion to become immunogenic. Additionally, excipients demonstrated diagnostic relevance with a positivity rate of 57.9%, higher than that of active ingredients (31.9%; p = 0.025). These findings reinforce the need to investigate components considered inert, such as carboxymethylcellulose or polysorbate,[37] and the importance of evaluating the medication in its entirety.[1]

The time interval between the acute episode and testing also proved to be a determinant, with the highest probability of diagnostic confirmation observed within two weeks of the event (OR 14.72; 95% CI: 1.78–121.2). This finding contrasts with international guidelines suggesting longer intervals[37] but finds support in the dynamics of resident memory T cells in FDE. As demonstrated by Shiohara et al.,[5] although CD8+ T lymphocytes persist at the dermo-epidermal junction, the progressive reduction of local inflammation may raise the activation threshold of these cells, decreasing test sensitivity when performed late.

PT positivity demonstrated a strong dependence on the application site, with significantly higher reactivity in lesional skin (19.2%) than in non-lesional skin (5.0%; p = 0.01). Even under simultaneous application at both sites, the

response remained almost restricted to the lesion, a finding widely supported by the literature. Andrade et al.[15] observed 40.4% positivity in residual lesions versus only 1.9% in healthy skin, while Phillips et al.[28] and Thaiwat et al.[22] reinforce that *in situ* sensitivity reaches 40-64%, being substantially lower in uninvolved areas. This discrepancy is directly supported by the pathophysiology described by Shiohara et al..[5] Trm persist specifically in previously affected areas. Thus, when applying the drug to uninvolved skin, where the density of these cells is minimal, the probability of reactivation and inflammatory response becomes significantly lower.

The vehicle used also demonstrated a significant impact on test performance ($p < 0.001$). A 100% positivity rate was observed with the use of DMSO, in contrast to 12.1% when petrolatum was used. Although petrolatum is traditionally recommended by international (ESCD and EAACI)[38] and national[26] guidelines, its permeation capacity may be insufficient for certain drugs.

Regarding the safety of diagnostic procedures, the PT presented a high tolerability profile in a sample of 310 cases. The majority of patients (96.7%; n = 297) had no complications beyond the expected test positivity. Local reactivation was observed in 3% (n = 9) of cases, while reactivation associated with fever was a rare event, identified in only 0.3% (n = 1). At first glance, this profile seems more favorable than that observed in the OPT, in which local reactivation occurred in 57.7% of cases and the appearance of new lesions in 4.1%. However, local reactivation is a non-serious adverse event, and the occurrence of new lesions remained low when considered alongside the higher diagnostic reliability of the method.

Open provocation demonstrated a diagnostic sensitivity of 92.1%, with cutaneous manifestations, primarily redness and erythema, observed in 66.7% of patients. Despite a higher frequency of local skin reactions, Phillips et al.[28] highlight that *in situ* open provocation (ROAT) constitutes a promising alternative when the occlusive PT is negative or when affected anatomical sites (such as oral or genital mucosae) are not amenable to standard occlusive testing.[28-31] The high performance metrics reported for this method should be interpreted with caution, as its perceived accuracy may be influenced by the relatively small sample size and a limited number of negative controls in the available literature. As a consequence, ROAT has not been supported in the literature as a substitute for oral provocation in the etiological investigation of FDE, particularly when the clinical decision depends on the safe exclusion of a culprit drug.

OPT, although remaining the gold standard for diagnosing drug eruptions, is frequently avoided due to the potential for adverse events.[17-21] In this review, however, the main effect observed was the local reactivation of the previously localized drug eruption, a scenario that may be acceptable in non-bullous forms with a limited number of lesions, since the appearance of new lesions was uncommon.

Although guidelines recommend PT as the initial approach in non-immediate reactions,[27] the findings of this review demonstrate that its performance in FDE is strictly dependent on technical and clinical variables, such as the application site, the vehicle, the time interval, and the investigation of metabolites or excipients. These elements are crucial for the correct interpretation of results and for defining the diagnostic strategy.

Limitations of the Study

This review has some limitations. The evidence base was dominated by single case reports and small case series, often without negative controls and with heterogeneous reporting of paired index-test and reference-standard data, limiting the robustness of pooled sensitivity and conditioning interpretation of high pooled specificity. QUADAS-2 assessment was restricted to the 25 studies included in the quantitative synthesis; the remaining 53 studies, mostly case reports without negative controls, did not meet the structural requirements for this tool, particularly for patient selection and flow and timing. The accuracy dataset included only non-immunosuppressed individuals, and comorbidities were absent or poorly reported, preventing assessment of host-related factors and precluding inference in immunosuppressed or clinically complex populations. ROAT specificity and patient-level patch-test specificity were based on only two and six paired negative controls, respectively, and should be interpreted descriptively. Substantial heterogeneity in sensitivity indicates that pooled sensitivity reflects a central estimate across variable study-level performances, while specificity findings cannot be extrapolated beyond represented populations. The search was restricted to publications from 1972 onwards, as prespecified in PROSPERO (CRD42024486891), so earlier reports may have been missed, although the impact is likely limited. Finally, infrequent testing of drug metabolites and excipients may have underestimated true reactivity, particularly for drugs dependent on metabolic conversion.

Conclusion

This systematic review with Bayesian meta-analysis suggests that patch testing in FDE has high specificity and a favorable safety profile, making it useful as a complementary or confirmatory tool for culprit-drug identification. However, its low and variable sensitivity means that negative results do not exclude drug causality, and current evidence does not support patch testing as a substitute for oral provocation testing. Its diagnostic value appears greatest when performed on previously lesional skin and when methodological variables such as timing, vehicle, concentration, and reading intervals are carefully considered. Larger prospective studies using standardized protocols and systematic assessment of metabolites and excipients are required to define its role more precisely.

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Supplementary files

Supplementary File 1: Search strategy used to identify articles in electronic databases

Databases	Search Strategy
LILACS	("Fixed drug eruption" OR "Fixed pigmented erythema" OR "Erupção fixa por drogas" OR "Eritema pigmentar fixo") AND ("Skin Tests" OR "Patch Test" OR "Patch Tests" OR "Testes cutâneos" OR "Teste de contato" OR "Testes de contato" OR "Topical provocation") AND ("Oral provocation" OR "Administração oral" OR "Oral Administration" OR "Oral Drug Administration" OR "Administração de medicamentos por via oral" OR "Teste de provocação" OR "Teste de provocação oral" OR "Drug Provocation Test" OR "Provocation Tests") **Filters applied:** 1972–2025. No language restriction was applied, as only one article was retrieved and it was published in Portuguese. Search conducted on October 21, 2025.
Embase	('fixed drug eruption':ti,ab,kw OR 'fixed pigmented erythema':ti,ab,kw) AND ('skin test'/exp OR 'patch test'/exp OR 'patch test':ti,ab,kw OR 'patch tests':ti,ab,kw OR 'testing, patch':ti,ab,kw OR 'topical provocation':ti,ab,kw) AND ('oral provocation':ti,ab,kw OR 'oral administration'/exp OR 'drug administration oral':ti,ab,kw OR 'oral drug administration':ti,ab,kw OR 'oral administration':ti,ab,kw OR 'oral administrations':ti,ab,kw OR 'oral drug':ti,ab,kw OR 'drug administrations':ti,ab,kw OR 'oral drug administrations':ti,ab,kw OR 'drug provocation test':ti,ab,kw OR 'provocation tests':ti,ab,kw) AND ([english]/lim OR [portuguese]/lim OR [spanish]/lim) AND [embase]/lim AND [1972-2025]/py **Filters applied:** Embase-published articles only; preprints excluded. Search conducted on October 21, 2025.
PubMed	("Fixed drug eruption"[tw] OR "Fixed pigmented erythema"[tw]) AND ("Skin Tests"[Mesh] OR "Patch Tests"[Mesh] OR "Patch Tests"[tw] OR "Patch Test"[tw] OR "Patch, Tests"[tw] OR "Testing, Patch"[tw] OR "Topical provocation"[tw]) AND ("Oral provocation"[tw] OR "Administration, Oral"[Mesh] OR "Drug Administration oral"[tw] OR "Oral Drug Administration"[tw] OR "Oral Administration"[tw] OR "Oral Administrations"[tw] OR "Oral Drug"[tw] OR "Drug Administrations"[tw] OR "Oral Drug Administrations"[tw] OR "Drug Provocation Test"[tw] OR "Provocation Tests"[tw]) **Filters applied:** Date range from 01/01/1972 to 30/09/2025; Languages: English, Portuguese, and Spanish. Search conducted on October 21, 2025.
Scopus	TITLE-ABS-KEY (("Fixed drug eruption" OR "Fixed pigmented erythema") AND ("Skin Tests" OR "Patch Tests" OR "Patch Test" OR "Patch, Tests" OR "Testing, Patch" OR "Topical provocation") AND ("Oral provocation" OR "Administration, Oral" OR "Drug Administration oral" OR "Oral Drug Administration" OR "Oral Administration" OR "Oral Administrations" OR "Oral Drug" OR "Drug Administrations" OR "Oral Drug Administrations" OR "Drug Provocation Test" OR "Provocation Tests")) AND PUBYEAR > 1971 AND PUBYEAR < 2026 AND (LIMIT-TO (LANGUAGE , "English") OR LIMIT-TO (LANGUAGE , "Spanish")) **Filters applied:** 1972–2025; languages: English and Spanish. Search conducted on October 21, 2025.

Web of Science	ALL=(("Fixed drug eruption" OR "Fixed pigmented erythema") AND ("Skin Tests" OR "Patch Tests" OR "Patch Test" OR "Patch, Tests" OR "Testing, Patch" OR "Topical provocation") AND ("Oral provocation" OR "Administration, Oral" OR "Drug Administration oral" OR "Oral Drug Administration" OR "Oral Administration" OR "Oral Administrations" OR "Oral Drug" OR "Drug Administrations" OR "Oral Drug Administrations" OR "Drug Provocation Test" OR "Provocation Tests")) **Filters applied:** January 1, 1972–September 30, 2025; language: English. Search conducted on October 21, 2025.

Supplementary files

Supplementary File 1: Search strategy used to identify articles in electronic databases

Databases	Search Strategy
LILACS	("Fixed drug eruption" OR "Fixed pigmented erythema" OR "Erupção fixa por drogas" OR "Eritema pigmentar fixo") AND ("Skin Tests" OR "Patch Test" OR "Patch Tests" OR "Testes cutâneos" OR "Teste de contato" OR "Testes de contato" OR "Topical provocation") AND ("Oral provocation" OR "Administração oral" OR "Oral Administration" OR "Oral Drug Administration" OR "Administração de medicamentos por via oral" OR "Teste de provocação" OR "Teste de provocação oral" OR "Drug Provocation Test" OR "Provocation Tests") **Filters applied:** 1972–2025. No language restriction was applied, as only one article was retrieved and it was published in Portuguese. Search conducted on October 21, 2025.
Embase	('fixed drug eruption':ti,ab,kw OR 'fixed pigmented erythema':ti,ab,kw) AND ('skin test'/exp OR 'patch test'/exp OR 'patch test':ti,ab,kw OR 'patch tests':ti,ab,kw OR 'testing, patch':ti,ab,kw OR 'topical provocation':ti,ab,kw) AND ('oral provocation':ti,ab,kw OR 'oral administration'/exp OR 'drug administration oral':ti,ab,kw OR 'oral drug administration':ti,ab,kw OR 'oral administration':ti,ab,kw OR 'oral administrations':ti,ab,kw OR 'oral drug':ti,ab,kw OR 'drug administrations':ti,ab,kw OR 'oral drug administrations':ti,ab,kw OR 'drug provocation test':ti,ab,kw OR 'provocation tests':ti,ab,kw) AND ([english]/lim OR [portuguese]/lim OR [spanish]/lim) AND [embase]/lim AND [1972-2025]/py **Filters applied:** Embase-published articles only; preprints excluded. Search conducted on October 21, 2025.
PubMed	("Fixed drug eruption"[tw] OR "Fixed pigmented erythema"[tw]) AND ("Skin Tests"[Mesh] OR "Patch Tests"[Mesh] OR "Patch Tests"[tw] OR "Patch Test"[tw] OR "Patch, Tests"[tw] OR "Testing, Patch"[tw] OR "Topical provocation"[tw]) AND ("Oral provocation"[tw] OR "Administration, Oral"[Mesh] OR "Drug Administration oral"[tw] OR "Oral Drug Administration"[tw] OR "Oral Administration"[tw] OR "Oral Administrations"[tw] OR "Oral Drug"[tw] OR "Drug Administrations"[tw] OR "Oral Drug Administrations"[tw] OR "Drug Provocation Test"[tw] OR "Provocation Tests"[tw]) **Filters applied:** Date range from 01/01/1972 to 30/09/2025; Languages: English, Portuguese, and Spanish. Search conducted on October 21, 2025.
Scopus	TITLE-ABS-KEY (("Fixed drug eruption" OR "Fixed pigmented erythema") AND ("Skin Tests" OR "Patch Tests" OR "Patch Test" OR "Patch, Tests" OR "Testing, Patch" OR "Topical provocation") AND ("Oral provocation" OR "Administration, Oral" OR "Drug Administration oral" OR "Oral Drug Administration" OR "Oral Administration" OR "Oral Administrations" OR "Oral Drug" OR "Drug Administrations" OR "Oral Drug Administrations" OR "Drug Provocation Test" OR "Provocation Tests")) AND PUBYEAR > 1971 AND PUBYEAR < 2026 AND (LIMIT-TO (LANGUAGE , "English") OR LIMIT-TO (LANGUAGE , "Spanish")) **Filters applied:** 1972–2025; languages: English and Spanish. Search conducted on October 21, 2025.

Web of Science	ALL=(("Fixed drug eruption" OR "Fixed pigmented erythema") AND ("Skin Tests" OR "Patch Tests" OR "Patch Test" OR "Patch, Tests" OR "Testing, Patch" OR "Topical provocation") AND ("Oral provocation" OR "Administration, Oral" OR "Drug Administration oral" OR "Oral Drug Administration" OR "Oral Administration" OR "Oral Administrations" OR "Oral Drug" OR "Drug Administrations" OR "Oral Drug Administrations" OR "Drug Provocation Test" OR "Provocation Tests")) **Filters applied:** January 1, 1972–September 30, 2025; language: English. Search conducted on October 21, 2025.

Supplementary Table 1: Studies included in the systematic literature review (n = 78).

Article number	First author, year	Article title	DOI	Type of study
1	Brehon et al., 2024	Doxycycline-induced fixed drug eruption: The new epidemic?	10.1111/jdv.20280	2
2	Gultekin et al., 2024	Nonsteroidal anti-inflammatory drug-induced fixed urticaria: first pediatric case report	10.1016/j.anai.2024.06.030	1
3	Terada et al., 2022	Hydroxyzine-induced fixed drug eruption and cross-reaction with oxatomide	10.1002/cia2.12275	1
4	Romero-Sánchez, Méndez-Brea, 2022	Fixed drug eruption due to clindamycin with tolerance to lincomycin	10.1111/cod.14164	1
5	Ercan, 2021	Mucosal fixed drug eruption to levetiracetam with early positive patch test on non-lesional skin	10.1111/pai.13723	1
6	Ammar et al., 2021	Fixed Drug Eruption Induced by Pristinamycin and Amoxicillin–Clavulanic Acid: An Unusual Case of Cosensitization	10.1097/DER.0000000000000775	1
7	Martínez Antón et al., 2020	Etoricoxib-induced fixed drug eruption: report of seven cases	10.1111/cod.13659	2
8	Ouni et al., 2021	Fixed drug eruption (FDE) induced by mefenamic acid with unusually cross-reactivity to diclofenac: A case report	10.1111/bcp.14448	1
9	Capilla et al., 2021	Fixed exanthema after the ingestion of naproxen with tolerance to ibuprofen and dexketoprofen	10.18176/jiaci.0518	1
10	de Castro et al., 2020	Allergy to beta-lactam antibiotics in children: risk factors for a positive diagnostic work-up	10.1016/j.aller.2020.01.005	1

11	Jamiolkowski et al., 2020	Multilocular bullous fixed drug eruption elicited by paracetamol and migraine attacks, but not by paracetamol alone	10.1111/cod.13567	1
12	Ammar et al., 2019	Celecoxib-induced bullous fixed drug eruption: An unusual presentation	10.1111/bcp.14072	1
13	Keskin et al., 2019	Case report: fixed drug eruption caused by dapagliflozin	10.25179/tjem.2018-63449	1
14	Labrosse et al., 2017	A pediatric case of selective fixed drug eruption to amoxicillin	10.1111/pai.12776	1
15	Ozkaya et al., 2017	Image Gallery: Purpuric fixed drug eruption from ornidazole showing leukocytoclastic vasculitis	10.1111/bjd.15823	1
16	Bellini et al., 2016	Bullous nonpigmenting multifocal fixed drug eruption due to pseudoephedrine in a combination drug: clinical and diagnostic observations	10.1016/j.jaip.2015.12.005	1
17	Lee et al., 2016	Fixed drug eruption due to acyclovir, valacyclovir and famciclovir	10.1111/jdv.13261	1
18	Heng et al., 2015	An update of fixed drug eruptions in Singapore	10.1111/jdv.12919	3
19	Ponvert et al., 2013	An unusual case of non-pigmenting fixed drug eruptions in a child	10.1111/pai.12116	1
20	Fukuda, Takahashi, 2019	S-Carboxymethyl-L-cysteine-induced fixed drug eruption	10.2340/00015555-3193	1
21	Kai et al., 2011	Fixed drug eruption caused by three unrelated drugs: promethazine, pethidine and omeprazole	10.1111/j.1365-2230.2011.04093.x	1
22	Gómez-Traseira et al., 2013	Paracetamol-induced fixed drug eruption at an unusual site	10.2174/1872213X113079990018	1
23	Ozkaya-Bayazit, 2004	Topical provocation in fixed drug eruption due to metamizol and naproxen	10.1111/j.1365-2230.2004.01537.x	4

24	Asano et al., 2021	Nonpigmenting and pigmenting fixed drug eruptions due to clarithromycin	10.1111/cod.13914	1
25	Sánchez-Morillas et al., 2008	Fixed drug eruption caused by amoxicillin–clavulanic acid	10.1016/s1081-1206(10)60501-7	1
26	Sánchez-Morillas et al., 2013	Fixed drug eruption due to norfloxacin and cross-reactivity with other quinolones	10.1016/j.aller.2011.10.004	1
27	Ammar et al., 2023	Cross-reactivity between nonsteroidal anti-inflammatory drugs in fixed drug eruption: two unusual cases and a literature review	10.1111/bcp.15565	2
28	Lee, 1998	Topical provocation in 31 cases of fixed drug eruption: change of causative drugs in 10 years	10.1111/j.1600-0536.1998.tb05739.x	4
29	Özkaya-Bayazit et al., 1999	Topical provocation in 27 cases of cotrimoxazole-induced fixed drug eruption	10.1111/j.1600-0536.1999.tb06127.x	3
30	Quint et al., 2019	Fixed drug eruption caused by fluconazole: an underdiagnosed but recurrent problem	10.1111/cod.13149	1
31	Keli-Bhija et al., 2015	An unusual case of penile non-pigmenting fixed drug eruption in a child	10.1111/pai.12361	1
32	Yokoyama et al., 2005	Multiple fixed drug eruption due to drug combination	10.1111/j.0105-1873.2005.0612b.x	1
33	Zedlitz et al., 2002	Reproducible identification of the causative drug of a fixed drug eruption by oral provocation and lesional patch testing	10.1034/j.1600-0536.2002.460606.x	1
34	Tornero et al., 2004	Clinical features, culprit drugs, and allergology workup in 41 cases of fixed drug eruption	10.1111/j.0105-1873.2004.00274.x	4
35	Lee, Lee, 1991	Provocation tests in a chlormezanone-induced fixed drug eruption	10.1177/106002809102500608	1
36	Kim et al., 2011	Fluconazole induced fixed drug eruption	10.5021/ad.2011.23.S1.S1	1

37	Handisurya et al., 2011	Fixed drug eruption caused by mefenamic acid: a case series and diagnostic algorithms	10.1111/j.1610-0387.2011.07621.x	2
38	Pérez-Calderón et al., 2011	Fixed drug eruption due to nabumetone in a patient with previous fixed drug eruptions due to naproxen	PMID 21462807	1
39	Gupta et al., 2010	Multiple fixed drug eruption caused by ornidazole	10.2310/6620.2010.10050	1
40	Morais et al., 2010	Nonpigmented fixed drug eruption induced by esomeprazole	10.3109/15569527.2010.484824	1
41	Iwabuchi et al., 2010	Fixed drug eruption induced by tipepidine hibenzate	10.1111/j.1346-8138.2010.00806.x	1
42	Gupta et al., 2009	Oral fixed drug eruption caused by gabapentin	10.1111/j.1468-3083.2009.03124.x	1
43	Ghosh et al., 2009	Clopidogrel-induced fixed drug eruption	10.1111/j.1468-3083.2009.03115.x	1
44	Felix et al., 2017	Hypersensitivity reactions to nonsteroidal anti-inflammatory drugs in children: report of two cases and review of new classifications	10.5935/2526-5393.20170060	1
45	Gupta et al., 2005	Fixed drug eruption caused by ornidazole	10.1111/j.0105-1873.2005.0654b.x	1
46	Martínez Alonso et al., 2005	Fixed drug eruption on the tongue due to clarithromycin	10.1111/j.0105-1873.2005.0650h.x	1
47	Adachi et al., 2005	Thiodiglycolic acid as a possible causative agent of fixed drug eruption provoked only after continuous administration of S-carboxymethyl-L-cysteine: case report and review of reported cases	10.1111/j.1365-2133.2005.06712.x	2
48	Goel, Jain, 2004	Fluconazole induced fixed drug eruption: a rare offender.	10.1111/j.1346-8138.2004.tb00683.x	1
49	Vilaplana, Romaguera, 2003	Fixed drug eruption from sodium benzoate	10.1111/j.0105-1873.2003.0265.x	1

50	Fujimoto, Tajima, 2003	Extensive fixed drug eruption due to the Japanese herbal drug “kakkon-to”	10.1111/j.1365-2133.2003.05676.x	1
51	Hayashi et al., 2003	Multiple fixed drug eruption caused by acetaminophen	10.1046/j.1365-2230.2003.01285_9.x	1
52	Kawakami et al., 2003	Dextromethorphan induces multifocal fixed drug eruption	10.1046/j.1365-4362.2003.01825.x	1
53	Pionetti et al., 2003	Fixed drug eruption due to loratadine	10.1016/s0301-0546(03)79199-x	1
54	Ruiz-Genao et al., 2002	Fixed drug eruption due to loratadine	10.1046/j.1365-2133.2002.46314.x	1
55	Hamamoto et al., 2001	Fixed drug eruption due to clarithromycin	10.1046/j.1365-2230.2001.00760.x	1
56	Jara et al., 2001	Allergic reactions due to ibuprofen in children	10.1046/j.1525-1470.2001.018001066.x	1
57	Sakakibara et al., 2001	Fixed-drug eruption caused by allylisopropylacetylurea	10.1034/j.1600-0536.2001.440308-10.x	1
58	de San Pedro et al., 2000	Fixed drug eruption caused by dimenhydrinate	10.1034/j.1398-9995.2000.00545.x	1
59	Özkaya-Bayazit, Güngör, 1998	Trimethoprim-induced fixed drug eruption: positive topical provocation on previously involved and uninvolved skin	10.1111/j.1600-0536.1998.tb05844.x	1
60	Mochida et al., 1996	Fixed drug eruption due to colchicine	10.1159/000246317	1
61	Schena et al., 1992	Bullous fixed drug eruption induced by vinburnine	10.1111/j.1600-0536.1992.tb05251.x	1
62	Habbema, Bruynzeel, 1987	Fixed drug eruption due to naproxen	10.1159/000249170	1
63	Tan, Copeman, 1974	Fixed drug eruption due to “nonabsorbable” sulphonamides	10.1177/003591577406700310	1

64	Pak, Vastardi, 2024	Fixed drug eruption: a case of successful treatment in a patient with recurrent trichomoniasis	10.1016/j.anai.2024.01.077	1
65	Choi et al., 2023	Fixed drug eruption in a patient taking valacyclovir without cross-reactivity to acyclovir	10.5021/ad.21.074	1
66	Rodriguez Gamboa et al., 2016	Fixed Drug Eruption to arylpropionic acids	10.1016/j.jaci.2015.12.147	1
67	Calvão et al., 2022	Patch testing in fixed drug eruptions: a 12-year retrospective study	10.1111/jdv.18290	2
68	Tsami et al., 2015	Atypical nonpigmenting fixed drug eruption caused by ciprofloxacin	10.1111/all.12723	1
69	Gaiser, Sabatino, 2013	Fluconazole-induced fixed drug eruption	PMID 23556037	1
70	Ozdemir et al., 2011	Fixed drug eruption due to meloxicam	PMID 21905514	1
71	Klos et al., 2010	Cutaneous adverse drug reactions to cetirizine	https://www.researchgate.net/profile/Susana-Armesto/publication/333203274_1232_Thyroid_Autoimmunity_and_Vitiligo/links/5ce1892c458515712eb693fb/1232-Thyroid-Autoimmunity-and-Vitiligo.pdf	2
72	Cadinha et al., 2009	Levofloxacin induced fixed drug eruption	https://www.researchgate.net/profile/Mohammad-Bemanian/publication/280731860_Mutation_analysis_of_the_NCF1_gene_in_chronic_granulomatous_disease_patients_with_the_P47-phox_deficiency_in_Iran/links/58b2898745851503b	1

			e9c04ea/Mutation-analysis-of-the-NCF1-gene-in-chronic-granulomatous-disease-patients-with-the-P47-phox-deficiency-in-Iran.pdf	
73	García et al., 2001	Allergic contact dermatitis due to deer-fat cream (Hirschtalgcreme)	10.1034/j.1600-0536.2001.440107-7.x	1
74	Fernández-Rivas et al., 1997	Fixed drug eruption caused by norfloxacin	10.1111/j.1398-9995.1997.tb01035.x	1
75	Schick et al., 1996	Topical and systemic provocation of fixed drug eruption due to phenazone	10.1111/j.1600-0536.1996.tb02280.x	1
76	Kawada et al., 1996	Fixed drug eruption induced by acetaminophen in a 12-year-old girl	10.1111/j.1365-4362.1996.tb03287.x	1
77	Kawada et al., 1994	Fixed drug eruption induced by ciprofloxacin	10.1111/j.1600-0536.1994.tb01962.x	1
78	Pareek, 1980	Nystatin-induced fixed eruption	10.1111/j.1365-2133.1980.tb01692.x	1

Legend: Study design: 1 = single case report; 2 = case series; 3 = retrospective study based on medical record review; 4 = prospective study.

Supplementary Table 2: Studies included in the diagnostic accuracy meta-analysis (n = 25).

First author, year	Article title	DOI	Type of study
Romero-Sánchez, Méndez-Brea, 2022	Fixed drug eruption due to clindamycin with tolerance to lincomycin	10.1111/cod.14164	1
Ammar et al., 2021	Fixed Drug Eruption Induced by Pristinamycin and Amoxicillin–Clavulanic Acid: An Unusual Case of Cosensitization	10.1097/DER.0000000000000775	1
Capilla et al., 2021	Fixed exanthema after the ingestion of naproxen with tolerance to ibuprofen and dexketoprofen	10.18176/jiaci.0518	1
Labrosse et al., 2017	A pediatric case of selective fixed drug eruption to amoxicillin	10.1111/pai.12776	1
Heng et al., 2015	An update of fixed drug eruptions in Singapore	10.1111/jdv.12919	3
Kai et al., 2011	Fixed drug eruption caused by three unrelated drugs: promethazine, pethidine and omeprazole	10.1111/j.1365-2230.2011.04093.x	1
Gómez-Traseira et al., 2013	Paracetamol-induced fixed drug eruption at an unusual site	10.2174/1872213X113079990018	1
Asano et al., 2021	Nonpigmenting and pigmenting fixed drug eruptions due to clarithromycin	10.1111/cod.13914	1
Ammar et al., 2023	Cross-reactivity between nonsteroidal anti-inflammatory drugs in fixed drug eruption: two unusual cases and a literature review	10.1111/bcp.15565	2
Lee, 1998	Topical provocation in 31 cases of fixed drug eruption: change of causative drugs in 10 years	10.1111/j.1600-0536.1998.tb05739.x	4
Quint et al., 2019	Fixed drug eruption caused by fluconazole: an underdiagnosed but recurrent problem	10.1111/cod.13149	1

Yokoyama et al., 2005	Multiple fixed drug eruption due to drug combination	10.1111/j.0105-1873.2005.0612b.x	1
Lee, Lee, 1991	Provocation tests in a chlormezanone-induced fixed drug eruption	10.1177/106002809102500608	1
Pérez-Calderón et al., 2011	Fixed drug eruption due to nabumetone in a patient with previous fixed drug eruptions due to naproxen	PMID 21462807	1
Iwabuchi et al., 2010	Fixed drug eruption induced by tipepidine hibenzate	10.1111/j.1346-8138.2010.00806.x	1
Martínez Alonso et al., 2005	Fixed drug eruption on the tongue due to clarithromycin	10.1111/j.0105-1873.2005.0650h.x	1
Ruiz-Genao et al., 2002	Fixed drug eruption due to loratadine	10.1046/j.1365-2133.2002.46314.x	1
Hamamoto et al., 2001	Fixed drug eruption due to clarithromycin	10.1046/j.1365-2230.2001.00760.x	1
Sakakibara et al., 2001	Fixed-drug eruption caused by allylisopropylacetylurea	10.1034/j.1600-0536.2001.440308-10.x	1
Mochida et al., 1996	Fixed drug eruption due to colchicine	10.1159/000246317	1
Choi et al., 2023	Fixed drug eruption in a patient taking valacyclovir without cross-reactivity to acyclovir	10.5021/ad.21.074	1
Gaiser, Sabatino, 2013	Fluconazole-induced fixed drug eruption	PMID 23556037	1
Cadinha et al., 2009	Levofloxacin induced fixed drug eruption	https://www.researchgate.net/profile/Mohammad-Bemanian/publication/280731860_Mutation_analysis_of_the_NCF1_gene_in_chronic_granulomatous_disease_patients_with_the_P47-phox_deficiency_in_Iran/lin	1

		ks/58b2898745851503be9c04ea/Mutation-analysis-of-the-NCF1-gene-in-chronic-granulomatous-disease-patients-with-the-P47-phox-deficiency-in-Iran.pdf	
Fernández-Rivas et al., 1997	Fixed drug eruption caused by norfloxacin	10.1111/j.1398-9995.1997.tb01035.x	1
Kawada et al., 1996	Fixed drug eruption induced by acetaminophen in a 12-year-old girl	10.1111/j.1365-4362.1996.tb03287.x	1

Legend: Study design: 1 = single case report; 2 = case series; 3 = retrospective study based on medical record review; 4 = prospective study.

5. CONCLUSÕES

Esta revisão sistemática, com meta-análise Bayesiana de acurácia diagnóstica, demonstra que o teste de contato no Eritema Pigmentar Fixo apresenta especificidade elevada e sensibilidade limitada, configurando-se como método confirmatório, porém insuficiente como ferramenta de exclusão diagnóstica. Entre os 78 estudos incluídos, apenas 25 forneceram dados estruturados adequados para análise quantitativa, evidenciando fragilidade metodológica relevante na literatura disponível, predominantemente composta por relatos de caso e pequenas séries.

A taxa global de positividade do *patch test* foi de 15,5% na amostra total de 310 testes. Quando considerados apenas os testes pareados com provocação oral, a sensibilidade foi de 24,85% e a especificidade de 94,92%.

A meta-análise estimou sensibilidade de 22% (ICr 95%: 6%–44%) e especificidade de 96,4% (ICr 95%: 89,8%–99,2%), com baixa taxa de falso-positivos (3,6%) e persistente proporção de falso-negativos. Esses achados confirmam que um resultado positivo possui elevado valor confirmatório, enquanto um resultado negativo não exclui a causalidade do fármaco.

Observou-se heterogeneidade importante entre os estudos, particularmente nas estimativas de sensibilidade, com desvio padrão entre estudos para o *logit* da sensibilidade de $\sigma 1 = 1,33$, em contraste com menor variabilidade para o *logit* da especificidade ($\sigma 0 = 0,43$). Esses parâmetros indicam variação substancial da sensibilidade entre os estudos incluídos, enquanto a especificidade se manteve mais estável. A performance diagnóstica

mostrou-se, portanto, heterogênea e fortemente dependente de variáveis metodológicas e clínicas.

Verificou-se variação substancial conforme a classe farmacológica, com melhor desempenho para anticonvulsivantes e anti-histamínicos e sensibilidade reduzida para antibióticos e outras classes. A baixa frequência de testagem de metabólitos e excipientes, associada à elevada positividade quando estes foram investigados, reforça a importância de abordagens diagnósticas que considerem o conceito de pró-hapteno e a participação de componentes não ativos na fisiopatologia das reações.

O intervalo temporal entre a erupção e a realização do teste mostrou-se determinante para a reatividade, com maior probabilidade de confirmação diagnóstica quando o teste foi realizado precocemente. De forma semelhante, a aplicação em pele lesional demonstrou maior taxa de positividade em comparação à pele não lesional, corroborando o papel das células T residentes de memória na manutenção da resposta local. O veículo utilizado também influenciou a performance do teste, evidenciando a relevância da penetração cutânea adequada para ativação imunológica.

No que se refere à segurança, o teste de contato apresentou perfil de alta tolerabilidade, com baixa taxa de eventos adversos relevantes. A provocação oral, embora associada a maior frequência de reativação local, manteve elevada capacidade diagnóstica e perfil predominantemente não grave na casuística analisada.

Em conjunto, os resultados desta tese evidenciam que o teste de contato, apesar de sua alta especificidade e segurança, apresenta sensibilidade limitada e forte dependência de variáveis técnicas e clínicas. A

ausência de padronização nos estudos primários, a escassez de dados estruturados e a heterogeneidade metodológica constituem obstáculos significativos à consolidação de recomendações definitivas. Esses achados reforçam a necessidade de estudos prospectivos, com amostras maiores e protocolos uniformizados, que incorporem sistematicamente a avaliação de metabólitos, excipientes, local de aplicação e momento ideal de testagem, visando otimizar a acurácia diagnóstica do EPF .

6. CONSIDERAÇÕES FINAIS

Os achados desta tese reiteram que o diagnóstico etiológico do EPF ainda carece de um método com sensibilidade equivalente ao TPO. Embora alguns resultados deste estudo contrastem com as recomendações de diretrizes internacionais (EAACI/ESCD), tais dados devem ser interpretados com cautela, dadas as limitações metodológicas inerentes à literatura disponível. Contudo, as evidências encontradas sinalizam a necessidade premente de se investigar novos protocolos para a realização de testes cutâneos, com atenção especial ao intervalo de testagem após a resolução da farmacodermia e ao veículo utilizado no *patch test*.

A análise de 310 testes cutâneos demonstrou que, embora o método apresente alta especificidade e um perfil de segurança favorável, sua sensibilidade é limitada e dependente de fatores que ainda não são padronizados. Nesse contexto, a positividade observada para excipientes e metabólitos demonstra que a investigação etiológica não deveria se restringir apenas ao princípio ativo, mas considerar o medicamento em sua totalidade. Da mesma forma, são necessários novos estudos para definir se o tempo de testagem preconizado atualmente é o mais adequado em termos de sensibilidade diagnóstica.

A identificação do intervalo de duas semanas como o período de maior probabilidade de positividade e o potencial aumento de sensibilidade com o uso do DMSO, visando a maior permeabilidade cutânea e solubilidade do fármaco, abrem frentes de investigação que podem otimizar o uso do teste de contato na prática clínica. Tais achados reforçam que as diretrizes atuais para o

diagnóstico etiológico de farmacodermias mediadas por hipersensibilidade tipo IV carecem de revisão e de uma estratificação específica para o EPF. O caminho para o refinamento deste diagnóstico reside na superação da fragmentação dos dados atuais, por meio de estudos prospectivos e multicêntricos que validem esses fatores técnicos e permitam uma aplicação mais assertiva e segura para o paciente.

7. APÊNDICES (Opcional)

A pesquisa foi originalmente concebida em 2018, sob o título "Avaliação dos testes in vivo e in vitro quanto à capacidade de identificação etiológica de farmacodermias". O projeto foi desenhado como uma cooperação entre o serviço de Dermatologia do HCPA e o Programa de Pós-Graduação da UFCSPA, com o suporte do serviço de Biomedicina desta mesma universidade.

O objetivo primordial era integrar a expertise clínica (testes de contato in vivo com fármacos e excipientes) a técnicas laboratoriais avançadas (teste in vitro ELISpot para identificação do fármaco causal). Contudo, devido a ajustes institucionais, a pesquisadora absorveu ambas as frentes de trabalho, tornando a análise in vitro o foco central do estudo naquele período.

Uma etapa significativa do doutorado foi dedicada à complexa padronização da extração de leucócitos (PBMCs) de pacientes com farmacodermias, visando manter a viabilidade celular necessária para o teste ELISpot. Iniciada em 2019, essa fase foi interrompida por cerca de um ano e meio devido à pandemia de COVID-19. Com a retomada em 2021, foi possível a inclusão de 20 pacientes até o ano de 2023.

Em 2023, após quatro anos de coleta e processamento, os testes ELISpot foram executados. No entanto, os resultados foram comprometidos pela não positivação do controle positivo da placa. A análise técnica indicou que, apesar do rigor nos protocolos, os leucócitos provavelmente perderam a viabilidade durante o longo período de armazenamento ou no processamento final. Devido ao extenso tempo de seguimento, não foi viável reconvocar os

mesmos pacientes para a realização dos testes de contato, o que inviabilizou a análise comparativa inicialmente pretendida.

Diante da impossibilidade de utilizar os dados laboratoriais para uma análise robusta, e mantendo o compromisso ético e científico com o tema, o projeto foi reestruturado. Decidiu-se pela realização de uma revisão sistemática com meta-análise, visando oferecer uma síntese das evidências globais sobre métodos diagnósticos no Eritema Pigmentar Fixo (EPF), garantindo uma contribuição relevante e baseada em evidências para a área da Dermatologia.

8. ANEXOS

8.1. PROSPERO

NIHR | National Institute for Health and Care Research

PROSPERO
International prospective register of systematic reviews

Evaluation of the skin patch test regarding the ability to identify the etiology of fixed drug eruption: a systematic review with meta-analysis

Fabiana Bazanella de Oliveira, Renan Rangel Bonamigo, Guilherme Ladwig Tejada

Citation 1 change
Fabiana Bazanella de Oliveira, Renan Rangel Bonamigo, Guilherme Ladwig Tejada. Evaluation of the skin patch test regarding the ability to identify the etiology of fixed drug eruption: a systematic review with meta-analysis. PROSPERO 2024 CRD42024486891. Available from https://www.crd.york.ac.uk/PROSPERO/view/CRD42024486891.

REVIEW TITLE AND BASIC DETAILS

Review title
Evaluation of the skin patch test regarding the ability to identify the etiology of fixed drug eruption: a systematic review with meta-analysis

Review objectives
Determination of drug culpability in fixed drug eruption can be challenging due to polypharmacy. Patch test and oral provocation are sometimes performed to identify the culprit drug, however the diagnostic accuracy and safety of these tests remain uncertain. Publications providing details of results of these tests will be reviewed to determine sensitivity, optimum concentration for testing as well as risk of reactivation after diagnostic tests like patch test and oral provocation.

SEARCHING AND SCREENING

Searches
MEDLINE, Embase and LILACS e databases will be searched for publications in English , Spanish and Portuguese, from 1972 onwards. Both keywords and subject headings will be

searched, with additions of relevant subject headings found in data indexes. Abstracts will be screened initially by 2 independent reviewers (FBO and GLT) and classified as 'include', 'exclude' or 'maybe' and concordant 'include' or 'maybe' articles reviewed. Additional reference list search of included publications will be performed. Data from individual publications will be extracted and results analyzed to determine accuracy, risk of adverse reactions, sensitivity, drugs which are suitable for testing with skin tests and non-irritant concentrations.

Study design
Prospective and retrospective case series and case reports with >1 case published from 1972 onwards will be included.

Link to search strategy 1 change
A full search strategy has been uploaded to PROSPERO. The PDF may be accessed through this link
https://www.crd.york.ac.uk/PROSPEROFILES/26ef5c480a5c0f494d534ffc871d5456.pdf.

ELIGIBILITY CRITERIA

Condition or domain being studied
Pigmented Fixed Drug Eruption (FDE) was first described in 1884 Since then, many cases have been described associated with the use of various medications. Despite not having a high prevalence in the population, can represent 7 to 21% of drug eruptions.
Clinically, it is described by the single or multiple appearance of rounded, violaceous or brownish erythematous lesions. The lesion usually resolves with hyperpigmentation on the body, but in the genital region it can resolve without leaving a trace. With each re-exposure to the medication, the patient may experience other lesions, which is why the etiological diagnosis of the drug is important There is a lack of data in the literature on possible causative drugs, as the etiological diagnosis is not always possible, especially when the patient is using multiple medications (polypharmacy) and if they have all been started at the same or similar periods in time.

Population
Studies in children and adults will be included. The characterization of fixed drug eruption can be clinical or confirmed by biopsy.
Subjects who have a test methodology different from the usual one, as removal of the patch in less than 48 hours and reading in less than 72 hours, will be excluded. As well as cases in which the included patients had used corticosteroids in the last 15 days.

Intervention(s) or exposure(s)
The data that will be extracted from the articles: first author, year of publication, type of study, number of patients with FDE, population characteristics (gender, presence or absence of comorbidities), time interval between drug eruption and testing, form of application of the test and other interventions performed, such as oral provocation testing. Special attention will be paid to the way in which the test is carried out (lesional or not - on the back), concentrations of the medications used and in which vehicle the drug was diluted, inclusion or not of excipient testing, how long the reading is carried out and whether more than one medicine was tested at the same time. The description of adverse effects reported after oral challenge or patch testing

will also be evaluated. Individual patient variables such as immunosuppression (HIV, transplant recipients) and their relationship with test positivity will also be evaluated.

Comparator(s) or control(s)

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.
Negative and positive controls are typically performed concurrently in individual participants in order to assess response to allergen tested.

OUTCOMES TO BE ANALYSED

Main outcomes

To evaluate the prevalence of oral challenge test positivity in patients with fixed drug eruption in relation to the prevalence of patch test positivity in the same population
Evaluate the prevalence of positivity for each medication in patch tests in patients with fixed drug eruption in order to assess whether there are drugs that are more inductive of skin test positivity when compared to others?
Evaluate whether there is a greater prevalence of positivity when the drug contact test is carried out on a lesional or non-lesional basis.
Evaluate whether there is a higher prevalence of patch test positivity in bullous or non-bullous fixed pigmentary erythema?
Assess whether there is a greater prevalence of positivity when using the commercial drug (with excipients) or the pure substance.
Evaluate the prevalence of positivity according to the period in which the test was performed after drug eruption(15 days, 30 days and up to 6 months later);

Additional outcomes

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

DATA COLLECTION PROCESS

Data extraction (selection and coding)

Abstracts that did not meet the inclusion criteria or that met the exclusion criteria will be discarded by 2 independent reviewers (FBO and GLT). The remainder of the records and those whose abstracts do not provide sufficient information to decide on their exclusion will be selected for full text evaluation, carried out by the same reviewers independently. A third reviewer (RRB) will resolve any differences.
Studies written in English, Portuguese and Spanish will be considered eligible if they contain sufficient information in English in the abstract, tables and figures.
We will carry out a systematic search in MEDLINE (via PubMed) and Embase and LILACS databases. Data that will be extracted from the articles: first author, year of publication, type of study, number of patients with FDE, population characteristics (gender, presence or absence of comorbidities), time interval between drug eruption and testing, form of application of the test and other interventions performed, such as oral provocation testing. Special attention will be

paid to the way in which the test is carried out (lesional or not - on the back), concentrations of the medications used and in which vehicle the drug was diluted, inclusion or not of excipient testing, how long the reading is carried out and whether more than one medicine was tested at the same time. The description of adverse effects reported after oral challenge or patch testing will also be evaluated. Individual patient variables such as immunosuppression (HIV, transplant recipients) and their relationship with test positivity will also be evaluated.

Risk of bias (quality) assessment

Publications with missing data, such as lack of information on total numbers of patients tested and how many were negative on testing will be removed to avoid publication bias. Review of publications will take place independently prior to discussion by the two researchers

PLANNED DATA SYNTHESIS

Strategy for data synthesis

A narrative and systematic synthesis from the included studies will be provided, focusing on the drugs and concentration to which tested with the corresponding results. A summary of the types of medications which give rise to positive results in comparison to those which never give rise to a reaction on skin testing. Also will be described if the positivity is lesional or non lesional, and the time between the drug eruption and the testing. Aggregated participant data will be used, as it is anticipated that there will be a small number of individual participants. Overall sensitivity, risk of adverse reactions and accuracy of skin test or oral provocation by medication will be calculated from the aggregated participants.

Analysis of subgroups or subsets

Subsets will be based on type medication tested, concentration of the medication, positivity of patch test, timing between the test and the eruption. Information on immunosuppression or conditions predisposing to this is included in publications, subgroup analysis will be performed for this group.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members

- Ms Fabiana Bazanella de Oliveira, UFCSPA
- Renan Rangel Bonamigo, UFRGS- Universidade Federal de Ciências da Saúde de Porto Alegre
- Guilherme Ladwig Tejada,

Review affiliation

UFCSPA- Universidade Federal de Ciencias da Saude de Porto Alegre

Funding source

None

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TIMELINE OF THE REVIEW

Review timeline
Start date: 01 February 2024. End date: 01 February 2026

Date of first submission to PROSPERO 1 change
01 February 2024

Date of registration in PROSPERO 1 change
12 February 2024

AVAILABILITY OF FULL PROTOCOL

Availability of full protocol 1 change
A full protocol has been written and uploaded to PROSPERO. The protocol will be made available after the review is completed.

CURRENT REVIEW STAGE

Publication of review results
The intention is not to publish the review once completed.

Stage of the review at this submission 1 change

Review stage	Started	Completed
Pilot work	✓	✓
Formal searching/study identification	✓	✓
Screening search results against inclusion criteria	✓	✓
Data extraction or receipt of IPD	✓	✓
Risk of bias/quality assessment	✓	✓
Data synthesis	✓	✓

Review status
The review is completed.

ADDITIONAL INFORMATION

PROSPERO version history 1 change

- Version 1.2, published 13 Mar 2026
- Version 1.1, published 12 Feb 2024
- Version 1.0, published 12 Feb 2024

Review conflict of interest
None known

Country
Brazil

Medical Subject Headings
Diagnostic Tests, Routine; Drug Eruptions; Humans; Patch Tests; Polypharmacy

Revision note 1 change
The inclusion and exclusion criteria were refined to better assess the diagnostic accuracy, sensitivity, and specificity of skin tests. Specifically, the updated protocol now requires the mandatory inclusion of studies where patients underwent both a skin test (patch test or topical provocation) and an oral provocation test (the gold standard) for the same drug. This adjustment was necessary to allow for a direct head-to-head comparison. Furthermore, all types of skin test reading methodologies and timeframes were included to ensure a comprehensive evaluation of the available evidence.

Disclaimer 1 change