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EAACI POSITION PAPER

EAACI/ENDA position paper on drug provocation testing

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Abstract

In drug hypersensitivity, drug provocation testing (DPT), also called drug challenge, is the gold standard for investigation. In recent years, risk stratification has become an important tool for adjusting the diagnostic strategy to the perceived risk, whilst still maintaining a high level of safety for the patient. Skin tests are recommended before DPT but may be omitted in low-risk patients. The task force suggests a strict definition of such low-risk patients in children and adults. Based on experience and evidence from studies of allergy to beta-lactam antibiotics, an algorithm on how to adjust DPT to the risk, and when to omit skin tests before DPT, is presented. For other antibiotics, non-steroidal anti-inflammatory drugs and other drugs, skin tests are poorly validated and DPT is frequently necessary. We recommend performing

Abbreviations: AGEP, acute generalized exanthematous pustulosis; Anti-TB, antituberculosis; ASA, aspirin; BAT, basophil activation test; BL, beta-lactams; COX, cyclo-oxygenase; CR, cross-reactive; CS, corticosteroids; DH, drug hypersensitivity; DHR, drug hypersensitivity reactions; DPT, drug provocation test; DRESS, drug reaction with eosinophilia and systemic symptoms; HS, hypersensitivity; IDT, intradermal test; Ig, immunoglobulin; IR, immediate reaction; IV, intravenous; MPE, maculopapular exanthema; NIR, non-immediate reaction; NSAIDs, non-steroidal anti-inflammatory drug; PT, patch tests; SCARs, severe cutaneous adverse drug reactions; SJS, Stevens–Johnson syndrome; SPT, skin prick tests; SR, selective responders; TEN, toxic epidermal necrolysis; TF, task force.

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DPT with chemotherapeutics and biologicals to avoid unnecessary desensitization procedures and DPT with skin tests negative contrast media. We suggest DPT with anesthetics only in highly specialized centers. Specifics of DPT to proton pump inhibitors, anticonvulsants and corticosteroids are discussed. This position paper provides general recommendations and guidance on optimizing use of DPT, whilst balancing benefits with patient safety and optimizing the use of the limited available resources.

KEYWORDS
beta-lactam antibiotics, delabeling, drug challenge, drug provocation test, risk stratification

1 | INTRODUCTION

Drug hypersensitivity reactions (DHR) account for an increasing number of referrals to allergy departments worldwide. Drug provocation testing (DPT), in other parts of the world, called drug challenge, is the gold standard of investigation, but only few published guidelines specifically address DPT.[1,2] Moreover, other guidelines on drug hypersensitivity (HS) investigation lack detailed and practical recommendations on DPT.[3,4]

The aim of this task force (TF) was to provide practical recommendations for DPT based on recent literature and expert opinion from TF members, who all have significant experience in DPT in both immediate and non-immediate drug hypersensitivity (DH). The paper comprises a section on general considerations concerning DPT and recommendations about DPT for specific drug groups. All the recommendations apply to both children (aged 18 years and below) and adults unless otherwise specified in the respective sections.

2 | METHODS

A literature search was performed with the key words #drug challenge, #drug provocation, #drug allergy/hypersensitivity/anaphylaxis and the names of the specific drug classes and individual drugs. A detailed table providing an overview of DPT protocols from studies identified from the literature for specific drug groups is provided (Table S1). The TF members had one physical meeting and six online meetings where recommendations were formulated, and consensus was achieved. The TF have applied GRADE-based recommendations.[5] A strong recommendation using the wording "the task force recommends" was made when there is confidence that the benefits do or do not outweigh harm and burden. A conditional recommendation using the wording "the task force suggests" indicated that the magnitude of benefit or not is less certain. Where evidence and experience were not sufficient to make a recommendation the wording "There is no recommendation for or against" was used. Each recommendation was discussed during on line meetings of the working group and included in the manuscript only when consensus (70%–89% agreement) or strong consensus (≥90% agreement) had been reached.

3 | GENERAL CONSIDERATIONS

For patients with suspected DHR, a detailed clinical history is crucial when planning investigations. In recent years, the concept of risk stratification has become an important tool for adapting the diagnostic strategy to the perceived risk and for optimizing investigations in terms of efficiency and resources, whilst still maintaining a high level of safety for the patient. So far, risk stratification has mainly been applied in suspected allergy to beta-lactam (BL) antibiotics.[6,7]

Investigations in drug hypersensitivity comprises detailed history, skin testing (skin prick test [SPT], intradermal test [IDT], patch test [PT] and in vitro testing specific immunoglobulins [Ig] E, basophil activation testing [BAT], lymphocyte transformation testing) and DPT. Different combinations of these tests are used depending on level of risk, the underlying mechanism, and whether an immediate (IR) or non-immediate reaction (NIR) is suspected. In mild to moderate maculopapular exanthemas (MPE), IDT with delayed reading seems of higher value than PT.[8,9] For details of other drug hypersensitivity investigations, we refer to the literature on the specific tests.[10–12]

Skin tests, and if negative, DPT should be done minimum 4 weeks after symptoms of the index reaction have subsided. The work-up can be carried out earlier in the case of emergency therapies such as chemotherapy, general anesthetics and antibiotics, but there are no large series available to assess the sensitivity and specificity of such early work-ups.[13] In drug reaction with eosinophilia and systemic symptoms (DRESS) a DPT with alternative drug should be done at least 6 months later.[8]

There is no maximum delay for the execution of a DPT. The best window of time is the year following the IR. But, even if the reaction is very far in the past, an allergy work-up can be carried out, even if it is less sensitive. In mild to moderate maculopapular exanthemas (MPE), IDT with delayed reading seems of higher value than PT.[8,9] For details of other drug hypersensitivity investigations, we refer to the literature on the specific tests.[10–12]

3.1 | Indications and contraindications for DPT

Indications, contraindications, and relative contraindications for DPT have been summarized in Tables 1 and 2. The TF recommends

TABLE 1 Indications for drug provocation tests (DPT).[1,7]

To exclude hypersensitivity to the suspected culprit drug when the history is non-specific or considered at low or intermediate risk of drug hypersensitivity. Removing the drug allergy label (delabeling) is especially indicated in allergy to penicillin as part of antibiotic stewardship and reducing antibiotic resistance
Cross-reactivity testing to find a safe alternative drug (from same or related drug group): in cases where drug skin tests/IgE/Basophil activation tests or DPT with the culprit drug is positive or not indicated, for example, due to severe reactions and high risk of allergy. Potentially safe alternative drugs should be identified on negative skin tests prior to DPT
To establish a robust diagnosis in the event of a history suggestive of drug allergy, but where other tests have been inconclusive or unavailable
When several drugs have been taken at the same time, to demonstrate tolerance to classes of drugs other than the identified culprit drug

TABLE 2 Contraindications and relative contraindications to drug provocation test (DPT).[1]

Contraindications for provocation test with suspected drug
In cases with a clear history of drug hypersensitivity when allergy was proven by other means such as skin tests or in vitro tests
With the suspected drug, in severe anaphylaxis (≥Grade 3) except in settings equipped for and experienced in performing high-risk provocations such as perioperative anaphylaxis
With the suspected drug, in generalized bullous fixed drug eruption
With the suspected drug, in toxic epidermal necrolysis (TEN) and Stevens–Johnson Syndrome (SJS)
With the suspected drug, in leucocytoclastic vasculitis
With the suspected drug, in Drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP)
Drug-induced specific organ dysfunction: cytopenia, hepatitis, nephritis, pneumonitis
Drug-induced autoimmune disease: systemic lupus erythematosus, linear IgA bullous dermatosis
Relative contraindications for provocation test with suspected drug
Severe comorbidity, for example, uncontrolled asthma, severe chronic obstructive airways disease, severe ischemic heart disease
Pregnancy—DPT can be performed when benefit of suspected drug outweighs the risk, such as severe infections (e.g., syphilis) and suspected penicillin allergy, or suspected local anesthetic allergy when spinal anesthesia may be needed for caesarean section

against DPT with the suspected drug in cases with a clear history of a DHR when allergy was proven by skin tests or in vitro tests, in cases of anaphylaxis except for highly specialized settings and in severe cutaneous adverse drug reactions (SCARs), except in some cases described below in the "special considerations" paragraph. DPT is relatively contraindicated during pregnancy and in cases of severe comorbidities Table 2.[1]

3.2 | Factors related to the patient and the setting of DPT

The TF recommends that:

1. DPT should be performed under medical supervision in a setting equipped for treating anaphylaxis including resuscitation equipment,[14] with personnel who are trained in performing DPT and in recognizing and treating potential symptoms of hypersensitivity including anaphylaxis.
2. DPT in intermediate and high-risk patients and patients with immediate-type symptoms should be performed in a hospital setting. Patients with mild MPE may be investigated with DPT in, or outside, a hospital setting in collaboration with allergy specialists.
3. The patient should be well on the day of DPT and baseline measurements of pulse, blood pressure and peak flow are recommended before drug administration, depending on risk assessment, and if symptoms arise. Intravenous (IV) access should be secured in high-risk patients with immediate reactions.
4. Verbal and written informed consent must be obtained before DPT.

The team should be capable of distinguishing stress-induced non-allergic symptoms from early signs of a DHR. The TF recommends that placebo-controlled DPT should be considered in patients suspected of having non-specific or subjective symptoms only. Depending on half-life, antihistamines and high dose systemic corticosteroids (>10 mg prednisolone daily) should be stopped before DPT, if possible. The TF suggests that antihistamines can be continued, if needed to control symptoms of chronic spontaneous urticaria and if DPT is urgently required. In cases where drug tolerance is demonstrated under antihistamine treatment, antihistamines should be applied before future administration of that drug. In case of permanent treatment with immunosuppressive or antidepressant drugs, a risk–benefit evaluation should be performed before interfering with this, due to the risk of other unwanted effects.

The TF can give no recommendation for or against stopping or pausing betablockers before DPT. However, the TF agrees that the risks of cardiovascular instability by stopping betablockers must be balanced against the questionable theoretical benefit of lowering risk and severity of anaphylaxis, which is lacking conclusive evidence. The TF does not recommend to stop angiotensin-converting-enzyme inhibitors before DPT.

3.3 | How to perform risk stratification

The planning of allergy investigations and need for DPT should be based on risk stratification including factors such as severity, suspected mechanism of the reaction, suspected drug, and clinical characteristics of the patient. See algorithm in Figure 1 and Table 3 for details of risk stratification and suggested management of patients.

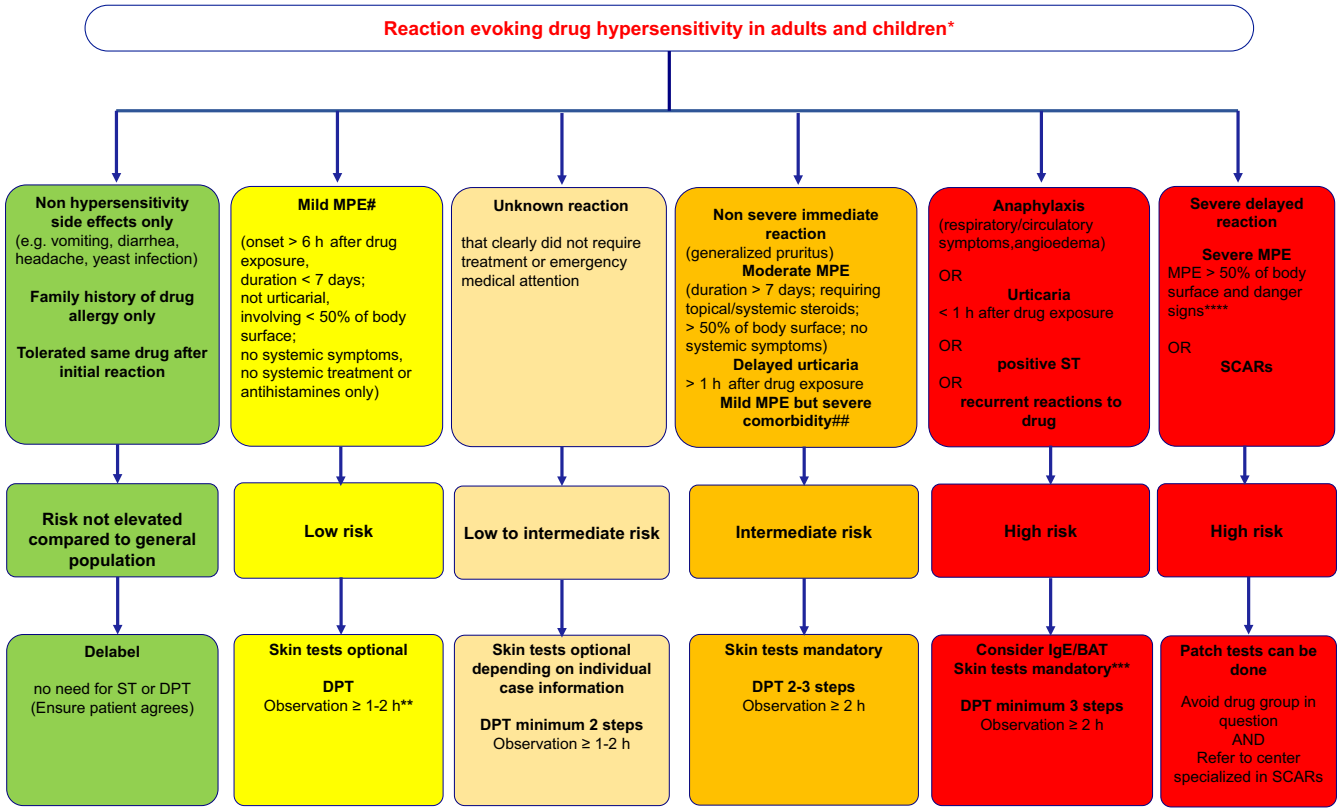

FIGURE 1 Algorithm for risk stratification from history and clinical features and recommended strategy for allergy work-up and drug provocation DPT.[7,15,16] *Not applicable in NSAID hypersensitivity (cross-reactors) – See Figure 2. DPT in intermediate and high-risk patients and patients with immediate-type symptoms should be performed in a hospital setting, whereas patients with mild MPE may be investigated with DPT in, or outside, a hospital setting in collaboration with allergy specialists. **Some pediatric centers practice 30 min observation. ***Unless specific IgE or BAT have confirmed the diagnosis. ****Danger signs in non-immediate reactions, according to Romano et al.[7]: intense facial involvement, atypical target lesions, bullous lesions, dark red erythema, extensive pustulosis, painful skin, mucosal involvement, generalized lymphadenopathy, elevated liver enzymes, impaired renal function tests, fever >38.5°C, alterations in blood cell counts (i.e., anemia, granulocytopenia, thrombocytopenia, neutrophilia, eosinophilia), hypocomplementemia, hepatitis, nephritis, and pneumonitis.BAT, basophil activation test; BL, beta-lactam antibiotics; DPT, drug provocation test; Ig E, immunoglobulin E; MPE, maculopapular exanthema; SCARs, severe cutaneous adverse reactions; ST, skin testing. #Full definition of mild MPE: Exanthema that is not urticarial, involving less than 50% of the body surface, without danger signs mentioned in **** above, occurring more than 6 h after the drug intake, of less than 7-day duration, and not requiring hospitalization or systemic treatment other than antihistamines. ##Comorbidity, for example, significant cardiac or pulmonary disease, mastocytosis. The measurement of the affected body surface is defined as follows: (1) The area involved typically adheres to the classical rules of calculation commonly used for SCORAD calculation. This includes 4.5% for the anterior and posterior sides of the face, anterior and posterior sides of the arms, 1% for each palm, 1% for the genital area, 9% for each side of the legs, and 18% for the anterior and posterior sides of the trunk. (2) Then, for each area, the percentage of the involved surface is calculated. In case of a MPE, you need to estimate the approximate percentage of red dots and normal skin.

These recommendations are based mainly on experience from the literature on allergy to beta-lactam antibiotics,[7,15–17] but the TF suggests that it may be applied in other drug groups.

3.4 | Route of administration and preparation used

When DPT is performed with the suspected culprit drug, it is recommended to use the exact product and the same route causing the initial reaction, if possible, to ensure exposure to the same excipients. In patients with severe DHRs to more than one drug/drug group or to specific drug groups, for example, depot corticosteroid preparations, reactions to excipients such as polyethylene glycol, carboxymethylcellulose and povidone should be considered.[18,19] When dilutions for DPT are needed, these can be prepared by hospital pharmacy or in the department. There is limited data on stability of drugs after dilution and the use of preservatives.[20]

The route of administration for DPT should be guided by initial reaction severity, patient comorbidity, and the setting where DPT is performed. Some advocate the route of administration from the initial reaction, and this is usually applied to injectable drugs for subcutaneous or intramuscular injection, for example, vaccines or local anesthetics. If a different route of administration is selected, attention should be paid to variation in excipients. Traditionally, it has been suggested that the oral route is the safest due to slower absorption and this is still the most used route.[1,3] The intravenous

TABLE 3 Risk stratification and recommendations regarding skin testing and drug provocation tests (DPT) according to risk profile.

Definitions of patient risk profiles	Recommendations regarding skin testing and DPT
Non-hypersensitivity reactions	
Well-known non-allergic adverse drug effects; full dose of same drug tolerated after initial reaction; allergy is only suspected in a close relative	Delabeling without skin testing or DPT
Immediate hypersensitivity reactions	
High-risk patient profile comprises: anaphylaxis, hypotension, laryngeal edema, bronchospasm, urticaria <1 h of drug exposure and/or angioedema, generalized flushing/erythema	Skin testing and, if available in vitro testing, must be performed DPT should only be considered if testing is negative
Intermediate risk: non-severe IRs, for example, generalized pruritus	Skin testing must be performed before DPT
Non-immediate hypersensitivity reactions	
High-risk patient profile Severe cutaneous adverse drug reactions (SCARs): Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), DRESS, acute generalized exanthematous pustulosis (AGEP), generalized bullous fixed drug eruption	DPT with a suspected drug is contraindicated In SCARs, drug patch tests can be done, and intradermal tests have to be discussed case by case by highly specialized teams
High-risk patient profile Non-SCARs: systemic vasculitis, linear IgA bullous dermatosis, specific drug-induced organ failures (e.g., hepatic, renal, pulmonary) or drug-induced autoimmune diseases	Drug skin tests are not useful
Intermediate risk patient profile comprises: • moderate MPE (lasting >7 days or requiring topical high potent/systemic corticosteroids, >50% of body surface, without systemic symptoms and without danger signs)[7] (Figure 1). • delayed urticaria with onset >1 h after drug exposure	Skin testing must be performed before DPT
Low-risk patient profile comprises: an exanthema that is not urticarial, with onset >6 h after drug intake, involving less than 50% of the body surface, of <7 days duration, without danger signs (no fever, lymphadenopathy, systemic involvement, blisters, mucosal involvement or eosinophilia), not requiring hospitalization or systemic treatment other than antihistamines	Skin testing is optional before DPT depending on individual case information
Unknown reaction	
Low-intermediate risk	Skin testing is optional before DPT depending on individual case information

Note: See also Figure 1.

(IV) route is associated with a risk of rapidly evolving reactions,[21] but in some specialized centers with experience in IV DPT in high-risk patients, it is suggested that the IV route, using incremental doses, is easier to control, as symptoms are likely to occur earlier during IV than oral administration and may appear after a smaller dose.[22] As the setting for DPT and experiences on safety differ between the authors, no recommendation is made concerning oral or IV routes for DPT.

3.5 | Dosing of DPT and observation time

Risk stratification should lead to decisions on starting dose, number of doses, dosing increments, time interval between doses (not less than 30 min intervals), observation time after the last dose and whether DPT should be continued over subsequent days. Some groups prefer to reach the cumulated daily dose, but the TF suggests that at least the maximum single therapeutic/unit dose should be reached. For example, for a drug taken at a dosing frequency of 500 mg three times a day, the target dose for DPT should be 500 mg (see Table S1 for details for specific drugs).

In the case of non-severe IR with skin symptoms only, the TF suggests that the starting dose should not exceed 1:10 of the single target dose. In cases of anaphylaxis, the TF suggests starting with a dose not exceeding 1:100 of the single target dose. In NIR, the TF suggests the starting dose is full dose or 1:10.

The observation time should be minimum 1–2 h after the last dose, depending on the individual risk for the patient, because severe reactions, such as anaphylaxis, usually occur during this time interval.[7,13] Longer observation periods may be considered based on delay in onset of the initial reaction, the risk to the patient and/or the drug kinetics, for example, for non-steroidal anti-inflammatory drugs (NSAIDs)[23] and proton pump inhibitors (PPIs).[24]

3.6 | Outcome assessment: Diagnostic criteria for a positive DPT and differential diagnosis

A positive DPT usually reproduces objective signs and symptoms compatible with the initial reaction (Table 4).[1,2,14] Subjective symptoms may precede objective ones. Young children often exhibit agitation or withdrawal behavior as initial symptoms prior to objective signs such

TABLE 4 Subjective symptoms and signs that may appear during drug provocation testing (DPT) and how to differentiate from allergic reaction.

Subjective signs and symptoms	Important clinical examination data
Dyspnea with normal auscultation and no skin/mucosal symptoms	Changes in respiratory rate, peak flow measurement and oxygen saturation may be helpful in identifying early signs of allergic reaction, often caused by hyperventilation. Blood gas analysis may be helpful in determining low CO_2 in hyperventilation
Pruritus or tingling-type paresthesias without skin/mucosal symptoms	But pruritus on lips, head and palms maybe the first manifestation of anaphylaxis.
Throat discomfort (feeling of swelling in throat or tongue)	Examine for edema, swallowing difficulty, hoarseness, stridor. Flexible nasoendoscopy may be helpful to rule out edema in pharynx/larynx in the acute phase
Isolated abdominal pain/nausea	Rarely an allergy symptom
Medicines such as local anesthetics frequently cause stress-related symptoms especially vasovagal reaction, hyperventilation, panic attack and anxiety which can be misdiagnosed as allergy symptoms	Continuous pulse monitoring may be helpful in identifying low pulse associated with low blood pressure in vasovagal reactions

as urticaria. Subjective symptoms, without accompanying objective symptoms, are more likely stress/anxiety-induced reactions (nocebo reactions) and may be difficult to differentiate from DHR.[25–27] Examples of such subjective non-allergic symptoms are summarized in Table 4. Nocebo reactions occur in 3% of patients, mainly females,[27] and are correlated with known anxiety/depression, history of severe drug reactions, multiple drug reactions or previous subjective reactions.[15,26]

Serum tryptase may be helpful in distinguishing between hypersensitivity and anxiety reactions, especially in severe cases. This is provided that the patient does not have a history or clinical features suggestive of mast cell activation syndromes or hereditary alpha tryptasemia. When compared with a baseline level an elevation of the acute tryptase level > (1.2 × baseline tryptase level) + 2 supports mast cell degranulation.

3.7 | Further actions after assessment

The TF recommends:

1. In case of positive allergy work-up:
   a. to give a warning card/drug allergy passport[28];
   b. in addition, electronic drug hypersensitivity/allergy reporting systems linked to electronic medical records/decision support systems, bracelet with QR code should be updated where available;
   c. to address potential cross-reactivity and identify safe alternatives to the identified culprit.
2. In case of negative DPT, to explain to the patient that the drug can be used and to remove the allergy label from all medical files (hospital and general practice).

3.8 | Special considerations

In patients with DRESS, only for the least suspected drugs, a gradual drug rechallenge has been proposed and evaluated through a single center study.[29] This should only be performed in departments highly specialized in managing SCARs. In DRESS induced by antituberculosis (anti-TB) drugs, very carefully sequential DPT with minimally necessary basic anti-TB drugs can be done when continuation of treatment is urgently needed.[30] In fixed drug eruption (FDE), DPT can be diagnostic in cases of negative in situ PTs and in situ repeated application tests.[4,31]

There is a theoretical risk of inducing tolerance during DPT, but this is considered low when performing DPT by increasing the dose by 10-fold steps, with intervals of 30 min or more.[32]

4 | DRUG PROVOCATION TESTING WITH SPECIFIC DRUG GROUPS

4.1 | Beta-lactam antibiotics

The approach to allergy to beta-lactam antibiotics has evolved compared to the more restrictive approach recommended previously.[7] Many examples of risk stratification and algorithms have been published recently.[7,33–42] Whilst focus remains on patient safety, individual risk stratification means, that in patients considered to be at low risk of allergy a diagnosis can be achieved with fewer resources. However, in the literature three main areas still lack consensus in the adult population:

1. What defines a low-risk patient?

This has been addressed in this position paper in Figure 1, Table 3 and Table S2.

2. The place of DPT without preceding ST in adults.

The need for investigations before DPT in patients with NIRs and a low-risk profile is the subject of much debate (Table 5). Regarding children, there is strong evidence based on multiple large studies to provide a firm recommendation for direct oral DPT without skin testing first in low-risk patients.[17,37,43–45]

TABLE 5 Arguments for performing drug provocation testing (DPT) with or without preceding skin testing (ST) in adult patients with non-immediate drug hypersensitivity reactions (DHR).

In terms of…	Arguments for performing ST before DPT (adults with low-risk non-immediate reactions)	Arguments for performing DPT without ST (adults with low-risk non-immediate reactions)
Approach	At an individual-based level, STs are useful in diagnosing non-immediate allergic DHR and thus in avoiding renewal of iatrogeny	At a population-based level, most patients who declare suspicions of DHR to beta-lactam antibiotics (BL) are proven not to be allergic; thus, delabeling by direct DPT is rapid and pragmatic[a]
Geographical variations in epidemiology of reported drug allergy Inclusion criteria and recruitment	Regions reporting higher prevalence of allergy (including anaphylaxis) and allergic profiles have been historically prone to perform stepwise classical allergy work-up (e.g., Southern Europe)	Regions reporting lower prevalence of allergy (maybe also lower severity) have been promoting a more pragmatic approach (e.g., Northern America, Northern Europe)[a]
Resources	Classic allergy work-up is a medical intervention aimed at being diagnostic, and not only pragmatically turned towards therapeutic subsequent interventions. Profiling an allergy to BL by ST gives better understanding of future tolerances of other BL	Sharing allergists' expertise needs simplification of the classic allergy work-up in order for it to be accepted and used by other health care workers, thus extending the number of patients with access to allergy work-up procedures
Health/logistic problems	High quality health systems perform more diagnostic tests to decrease patient's risk of reacting upon re-exposure	Health systems with lower proportion of allergists or resources have more pressure to develop simpler procedures. However, it is crucial that patient safety is not compromised
Risk stratification	Definition of "low-risk" is clinical and does not always foresee a positive allergy work-up (see "general considerations" paragraph). A proportion of patients with positive skin test result have unknown/poorly defined reactions. According to an individual risk–benefit analysis, ST could be favored in patients with severe comorbidities even if their history is that of a low-risk reaction	There is no strict consensus on risk stratification criteria and criteria vary according to different studies. Moreover, risk stratification should take into consideration factors non-related to the reaction itself, such as patient status (pregnancy, underlying comorbidities). See Figure 1 and Table S2 for suggested criteria and literature overview
Safety in preventing a severe reaction upon rechallenge	In rare cases, IgE sensitization/allergy is revealed by ST or specific IgE testing	In most cases/publications, reactions elicited by direct DPT are mild /moderate[a]

Note: See Tables S1 and S2 and general considerations paragraph.

[a]Different inclusion criteria and recruitment bias the reporting and interpretation of prevalence of drug allergies across the world. In studies from specialized drug allergy centers, prevalence and severity of reactions is generally higher. However, when a delabeling approach is favored, with recruitment in general departments, prevalence and severity are lower.

In adults, there is increasing evidence that such an approach could be safe in targeted populations.[15,16,46–48] An overview of recent studies on direct DPT without previous skin testing in non-severe NIR in adults is summarized in Table S3. From these studies, among 5948 adult patients who had penicillin DPT without ST, 289 reactions (4.9%) occurred with only 2 cases of anaphylaxis (0.03%).

In adults with NIR where a drug allergy expert has performed a risk evaluation and considers the risk of a reaction on DPT to be low- as defined in Table 3 and Figure 1- the TF suggests that there is enough evidence to consider DPT, without skin testing first.

3. The value of prolonged DPT

Prolonged DPT exceeding 1 day for NIR diagnosis is also the subject of much debate.[39,46,49–52] There are many different protocols for performing prolonged DPT and there is no consensus on a preferred procedure. Details of all analyzed studies and their references are reported in Table S4. From 23 articles, including 6484 patients with prolonged DPT, reactions occurred in 495/6484 (7.6%); during the initial DPT in 147/6484 (2.3%) and during the prolonged DPT in 347/6337 (5.5%). As there is only one study with a washout period[50] presently, it is difficult to conclude if prolonged DPT increases sensitivity. Some studies suggest that the patient would be more likely to take the drug in the future after a prolonged DPT,[16] but others find a higher rate of refusal of further intake in the prolonged DPT group.[53] Arguments for one-day versus prolonged drug provocation test are summarized in Table S5. Based on the literature, at the present time the TF cannot make a recommendation for or against performing prolonged DPT.

The TF suggests that *if* prolonged provocation is performed in NIR:

- at least the maximum single therapeutic/unit dose should be reached;
- a washout period should be introduced between doses, to allow the initial dose to potentially elicit a reaction. There is some evidence that the initial dose can elicit reactions up to 48 h–7 days

later,[42,52] and ideally a minimum 48 h wash out period should be respected. However, to ensure patient compliance and/or assess risk of NIR, some groups perform prolonged DPT for 2–4 days[16,43] with a wash out period between initial dose and the following morning, that is, 16–18 h;
- DPT approaching the duration of a full treatment (7–10 days) is not recommended.

In the case of antimicrobial allergy, the risk of developing antimicrobial resistance with prolonged DPT must be weighed against the benefits of delabeling inaccurate drug allergy labels. In patients with severe IR to BL more than 6 months before investigation, who display negative results on IgE, skin tests and DPT, a risk of resensitization should be considered.[7] To identify resensitization in remote IRs, few highly specialized centers perform prolonged DPTs on this indication, on an experimental basis, and advice re-testing with ST or IgE tests 4–6 weeks later.[54]

4.2 | Non-beta-lactam antibiotics

4.2.1 | Macrolides

HRs to macrolides are rare. Skin tests are often irritant and badly standardized. In most cases DPT is needed to confirm or rule out hypersensitivity and to investigate cross-reactivity.[55,56]

4.2.2 | Fluoroquinolones

Although older data state that skin tests with fluoroquinolones (FQ) can be irritative[10] and that up to 50% of case may show cross-reactivity,[57,58] a new method for IDT reading has been recently suggested.[59] The authors studied 163 allergic sequential patients with an history of HS to FQ. Intradermal tests were performed according to ENDA protocol[12] using histamine as a positive control at a concentration of 0.1 mg/mL. For IDT to ciprofloxacin, levofloxacin, and moxifloxacin concentrations of 0.025 and 0.005 mg/mL were used. Authors considered negative tests those with non-specific wheal without flare which frequently occurs to multiple skin tested patients to FQ. 159 patients were negative using this criteria and 82/82 of them underwent single dose DPT to the index FQ or other FQ (levofloxacin 250 mg, ciprofloxacin 250 mg, moxifloxacin 200 mg).[59] Negative oral DPT resulted in the removal of FQ allergy or revision to confirm tolerance of an alternative FQ, as it is known that FQ may cross-react, Protocols vary in terms of doses and steps used, but most achieve full therapeutic dose in 1 or 2 days.[58]

4.2.3 | Sulfonamides

Krantz et al.[60] challenged 204 patients with low-risk IR and NIR, without allergy work-up, in a one- or two-step single dose procedure with tolerance of the drug in 94%.

4.2.4 | Metronidazole

Literature is based on small case series. Skin tests show low sensitivity and DPT is needed to confirm the diagnosis.[61]

4.2.5 | Tetracyclines

Infrequent use of tetracyclines results in very low rates of hypersensitivity primarily with FDE and photosensitivity, but also cases of DRESS.[62] Very few graded DPT have been reported.[62]

4.2.6 | Lincosamides

IR are rare, and NIR occur from <1% to 10.5%, including SCARs. There are only few reports with graded oral DPT.[63]

4.2.7 | Glycopeptides

Vancomycin and teicoplanin can induce anaphylaxis, MPE, vasculitis and SCARs. Non-allergic reactions to vancomycin (red man syndrome, Vancomycin flushing syndrome) occurs in 5%–14% of patients usually due to rapid infusion. Symptoms are itching and rash typically of face, neck and upper body caused by direct release of histamine from mast cells and basophils. It can typically be overcome by slowing infusion rate and premedication with antihistamine., Cross-reactivity between vancomycin and teicoplanin may occur.[64] DPT is rarely needed.[65]

4.2.8 | Aminoglycosides

One study reported graded intravenous DPT with gentamicin in skin test negative patients with IR.[66]

4.2.9 | Antituberculosis drugs (anti-TB drugs)

Data on HSs to anti-TB drugs are limited, but one study reported reactions in 3%–4% of patients.[67] HSs are usually benign MPEs, occurring few weeks after starting therapy. Some patients develop HS to multiple anti-TB drugs. A pragmatic approach to standardize the management is needed. When a HS occurs, all anti-TB drugs should be withdrawn, and skin testing should be performed.[68]

In NIR, the TF suggest that when skin tests are negative, all necessary anti-TB drugs may be sequentially re-introduced (rechallenge or graded escalation procedure) at an interval of 3–4 days, at target therapeutic doses, allowing time to detect a severe NIR with minimal risk of drug resistance. Details on skin tests and procedures with anti-TB drugs are given in Table S6.

4.3 | NSAIDs and paracetamol including children

NSAID hypersensitivity can be allergic with selective responders (SR) or non-allergic with cross-reactive patients (CR). DPT is used to confirm sensitization, study cross-reactivities or find alternatives.

Different protocols have been suggested.[23,69–76] In reviewed original studies (17 exclusively in children), 2374 adults, 3363 children and 100 not specified cases were included (Tables S7–S9). Most subjects (76.9%) were CR. In all patients, 19.7% of DPTs were positive, with a higher percentage in subjects confirmed as CR (23.3%) than in those confirmed as SR (8.6%).

Skin tests were rarely performed and were only carried out with culprit NSAID before DPT in 93 cases. In most studies, DPT was performed with an alternative NSAID (95%). Only 55.4% were tested with the culprit, and 50% were tested with culprit and alternative. The culprit drug was tested more frequently in SR (96.3%) than in CR (43.2%) and more often in children.

The DPT mainly tested positive for pyrazolones (in 65.7% subjects) and diclofenac (in 42.1%). The results of DPT for other NSAIDs are shown in Table S7.

In CR cases, skin tests are not helpful, and DPT with aspirin (ASA) or other NSAIDs are recommended to determine tolerance. In CR cases, cofactors such as preexisting CSU, asthma, mastocytosis can negatively influence the intensity of adverse effects and must be considered before DPT. In preexisting CSU, DPT with COX-2 inhibitors or preferential COX-2 inhibitors (nimesulide, meloxicam) can be done under concurrent antihistamine treatment. DPT with COX-1 inhibitors might be done after complete remission of CSU. In NSAID-exacerbated respiratory disease there is a risk of severe bronchospasm and graded DPT must be conducted cautiously. For CR patients, the sequence of NSAIDs given for DPT vary greatly in the literature. The test plan should consider the probability of inducing a reaction, which is lowest for selective COX-2 inhibitors ("coxibs"), and lower for partial COX-1 inhibitors (e.g., paracetamol)[77] than for full COX-1 inhibitors (e.g., ibuprofen, ASA).

The DPT dose increments are shown in Table S9. In 104 cases, the NSAID was administered as a single dose. The drug was administered at 90 min-interval in most cases (1117; 53.2%), followed by 60 min-intervals (546; 26%) and 120–180 min-interval (375; 17.8%). Although they may reduce the intensity of adverse effects of a DPT with NSAIDs/paracetamol, in well-controlled CSU patients, the TF suggests maintaining treatment with antihistamines or anti-IgE, as well as maintaining treatment with leukotriene agonists in patients with well-controlled asthma. A decision algorithm for NSAID-induced urticaria/angioedema is provided in Figure 2.

4.4 | Proton pump inhibitors (PPI) and antacids

DHR to proton pump inhibitors (PPIs) and Histamine-2-receptor antagonist (H2RA) have increased in the last decade. Most reactions to PPIs are IR[78] and skin test specificity is high, but sensitivity is low (22.6%–58.8%) thus DPT is necessary[79] when skin tests are negative. Single-blind, placebo-controlled DPT has been performed in skin test-negative patients, with the culprit in low and intermediate risk cases and with an alternative after severe reactions.[78–81] Titration and dosing were similar in all studies reaching full single dose in 1 day (Table S10).[24,78–80] Time interval between the incremental doses ranged from 30 to 60 min.[24,79–80] Cross-reactivity is reported among different PPI belonging to the same subgroup (Table S10), but patterns are variable and inconsistent.[24] Rabeprazole is in the "lansoprazole" group as esomeprazole and pantoprazole are in the "omeprazole group". Most PPIs are slow release and dose titration is challenging due to the formulation and potential loss of drug function. Due to the slow release, HRs may be delayed. Consequently, the TF suggests prolonged observation of ≥3 h after the last step of an oral DPT with PPI. IV DPT might be an option, but there is very limited experience with this approach.

PPI also induce NIR ranging from mild MPE to SCARS, but data on IDT with delayed reading and patch testing are limited. Cross-reactions to all PPI have been reported in DRESS.[81,82] For H2RA, DPT has been performed with 2–6 steps with 30-min intervals until the single therapeutic dose was reached in 1 day (Table S11).[83] Cross-reactivity between ranitidine and nizatidine has been found.[84] Data about non-immediate reactions are scarce.

The task force recommends to

1. perform DPT with the culprit PPI in patients with IR and negative skin test to the culprit;
2. perform DPT with alternative skin test-negative PPIs in patients with positive skin test to the culprit and in patients with a high-risk of severe anaphylaxis;
3. extend the observation time for oral DPT due to unpredictable absorption with the delay of the initial reaction.

4.5 | Iodinated and gadolinium-based contrast media

A negative skin test to iodinated (radio-)contrast media (ICM) cannot exclude hypersensitivity in all patients with ICM reaction. However, negative skin tests are associated with less severe non-allergic reactions and positive skin tests with more severe (and dangerous) allergic reactions.[85–99] DPT have been performed by allergists particularly after more severe reactions, which are often associated with positive skin tests, whereas ICM re-exposure conducted by a radiologist at the next needed x-ray/CT scan has been the traditional option for non-severe reactions (e.g., isolated urticaria or non-severe maculopapular exanthema) to confirm tolerability.[85] During the last decade DPT protocols have also been established[85–99] (Table S1).

Protocols for DPT with ICM are neither standardized nor validated; there is no consensus regarding dose and dose increments.[85] Series including up to 161 adult patients reported various modalities and doses for DPT. Maximum single doses ranged from 10 to 120 mL, dose increments from 1 to 7 steps, duration from 1 to

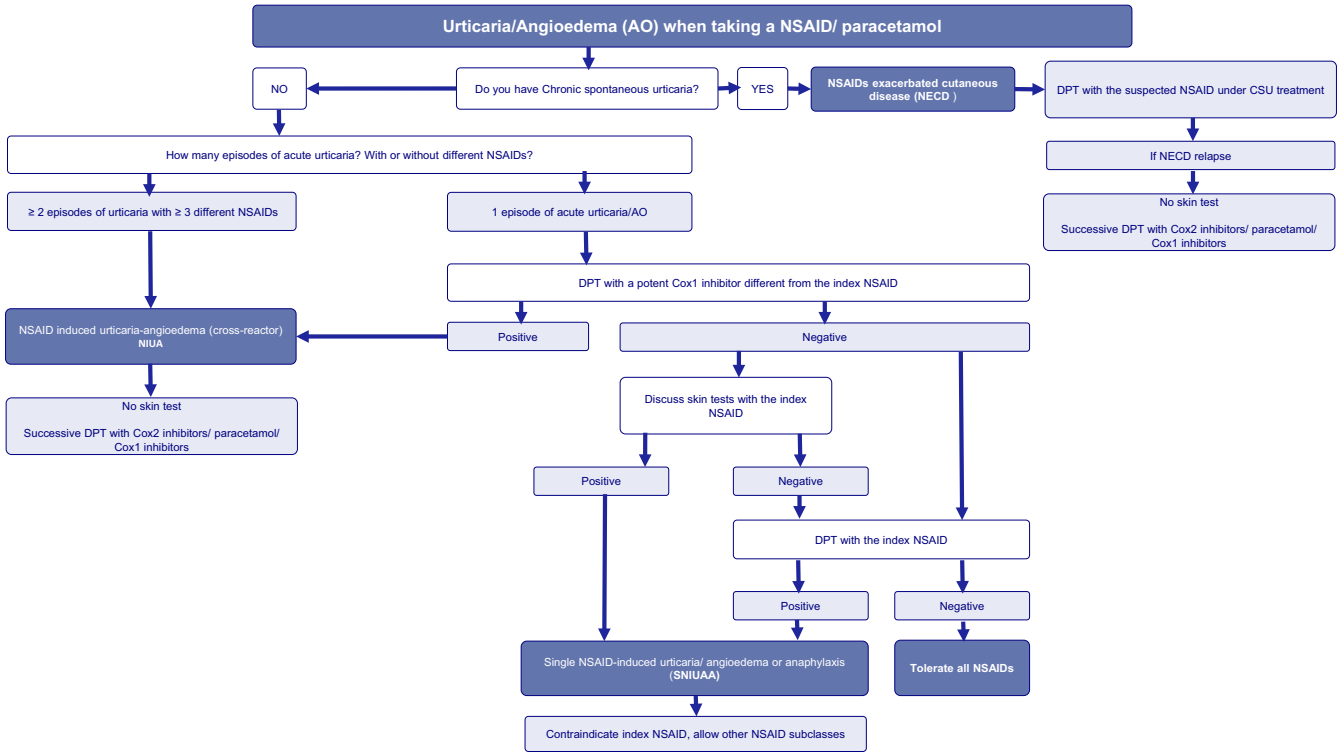

FIGURE 2 Decision algorithm for non-steroidal anti-inflammatory drug (NSAID)-induced urticaria or angioedema.

2 days. The second day in NIR was separated by 1–2 weeks in two centers[89,95] (Table S12). Intervals between doses were 30–120 min for IR and 60–1440 min for NIR. All studies performed DPT with skin test negative ICM and most used an alternative ICM, while some challenged the culprit ICM when negative in skin tests. One study, most likely using re-exposure in combination with premedication, re-exposed skin test positive non-culprit ICM and confirmed a high positive predictive value.[99] There is no evidence to recommend optimal doses for ICM DPT.

1. The TF recommends that both ICM re-exposure with an alternative skin test negative ICM by a radiologist, or DPT in an allergy department with a skin test negative alternative or culprit ICM, are both valid options depending on the risk involved for patients needing further ICM examinations. Patients with severe anaphylaxis should receive DPT in an allergy department, whereas for those with non-severe reactions, such as urticaria or MPE and negative skin testing an alternative ICM can be re-exposed in the radiology department according to the recommendations issued by the allergist.
2. ICM can cause acute kidney damage. The TF recommends excluding contraindications before DPT. Higher risk is seen in patients with reduced renal function; therefore, low-osmolality/iso-osmolar ICMs should be used, and oral serum bicarbonate, oral N-acetylcysteine, and/or intravenous saline solution (0.9%) may be given as prophylaxis[90] also before DPT.[97]

For gadolinium-based contrast media, there is only one low-dose one-step study performing DPT with 1 mL skin test-negative gadoteric acid in 14 patients.[100] The risk of inducing other adverse effects like nephrogenic fibrosis must be balanced against the need for DPT. Evidence is insufficient for recommending a specific protocol.

4.6 | Chemotherapy and biologicals

Rapid drug desensitization (RDD) is presently the main therapeutic approach to HSRs to both monoclonal antibodies (mAbs) and chemotherapeutics. However, emerging data suggests DPT might prevent a significant number of patients from undergoing unnecessary RDD.[101–103]

For chemotherapeutics, studies report negative DPT in 30%–56% of patients who could receive treatment without RDD.[101,104] Patients with paclitaxel HSR tolerated rechallenge more often than those with platin HSRs.[105] When multiple drugs are administered simultaneously, they should all be considered and DPT might prevent misdiagnosis. Leucovorin was the culprit in up to 11% of "oxaliplatin-reactive" patients.[106]

Limited data on DPT with mAbs have been published. In patients with unequivocal history of a DHR to mAbs, 30% showed negative DPT and could avoid RDD.[101] DPT protocols exist for rituximab, anti-TNF agents, trastuzumab and omalizumab. A diagnostic algorithm for DHRs to biologicals has been proposed.[103]

For both chemotherapeutics and biologicals, risk management strategies and contraindications follow general recommendations (Table 2). A risk stratification approach to rechallenge patients has been developed by Picard et al.[104] (Table S13).

DPT should only be performed if there is therapeutic indication for the drug. It is considered a high-risk procedure.[101] The patient's next scheduled treatment should be used for DPT, avoiding delays or overdose. The standard approach involves administering the infusion under normal conditions. Intensified premedication is not recommended.[102,103]

1. The TF recommends following previous guidelines proposed by EAACI.[102,103] For chemotherapy, the TF recommends performing DPT in moderate-low severity IR according to Picard et al.[104] (Table S13) with negative skin tests or negative BAT and normal serum tryptase. A RDD is recommended in high-risk patients with severe reactions, positive skin tests, or cardiovascular or respiratory comorbidities.
2. For biologicals, the TF suggests DPT in expert drug hypersensitivity centers, if the biological cannot be substituted with other skin test- and/or BAT-negative agents. In practice, the heterogeneity of DPT protocols between centers renders data comparison difficult and a standardized procedure has not yet been agreed.

4.7 | Perioperative drugs (NMBA, anesthetic agents, opiates, blue dyes, local anesthetics)

4.7.1 | Anesthetic drugs

DPT with potent anesthetic drugs, for example, hypnotics and neuromuscular blocking agents should only be performed in highly specialized centers in close collaboration between anesthetists and allergists.[20] Readers with a specific interest in DPT with drugs used exclusively in the perioperative setting are referred to literature specifically addressing this.[22,107]

4.7.2 | Opioids

Opioids rarely cause IgE-mediated allergic reactions but may induce direct mast cell histamine release via the opioid receptor or the MRGPRX2 receptor.[108,109] This is common with natural opioids, for example, morphine and codeine, and rare with synthetic opioids, for example, tramadol or fentanyl.[108] Opioids elicit gastrointestinal adverse effects, itch or rash often misinterpreted as allergy. A risk stratification algorithm for investigation of suspected opioid allergy has been suggested.[109] Skin testing using non-irritant concentrations[20] is useful for synthetic opioids, but shows limited usefulness for natural opioids.[110] Titrated DPT with opioids has been shown to be safe in experienced hands.[108]

4.7.3 | Local anesthetics

True allergic IR to local anesthetics (LA) are extremely rare. Vasovagal reactions, hyperventilation/anxiety attacks or toxicity symptoms may mimic hypersensitivity, but skin symptoms are typically missing.[111,112]

Skin testing is recommended before DPT when hypersensitivity is likely, or when patients need reassurance. Due to a high level of anxiety a placebo-controlled DPT should always be considered.[112] Cross-reactivity has been reported in both IR and NIR to LA and a skin test and DPT-negative alternative LA should always be identified,[111] ideally for both dental treatment and regional anesthesia.

LA provocation with vasoconstrictor to reproduce symptoms such as tachycardia, may reassure patients that such symptoms are benign.[112]

4.7.4 | Blue dyes

Most common dyes are patent blue and methylene blue used for sentinel node procedures in cancer surgery. Skin testing is gold standard and there is currently no provocation model.

4.8 | Corticosteroids

Provocation tests with corticosteroids (CS) should be performed at least 1 week after skin tests, as patch tests and IDT can show delayed positivity.[113,114] In case of IR to depot corticosteroid preparations, reactions to excipients, most commonly polyethylene glycol or carboxymethylcellulose, must be ruled out.[115] Anaphylaxis to methylprednisolone may be restricted to this corticosteroid, as cross-reactivity is unpredictable, a skin test- and DPT-negative alternative CS must be found in both IR and NIR.[114] The route of administration depends on patient need, and DPT with injectable steroids is usually performed intramuscularly or intravenously. Graded administration to reach the full dose or up to 1 mg/kg/day has been suggested[116] (Table S1).

4.9 | Anticonvulsants

Anticonvulsants are classified as aromatic and non-aromatic (Table S14).[117] They mainly induce NIR, with a high frequency of SCARs. In NIR, cross-reactivity between anticonvulsants is frequently reported between aromatics but cross-reactivity between aromatic anticonvulsants and lamotrigine, remains controversial.[118,119] Most studies were based on cases of DRESS, known for its high risk of multiple sensitizations without relation to chemical structures. Finally, some severe reactions could be explained by accumulation of toxic metabolites.

Non-aromatic anticonvulsants such as benzodiazepines, gabapentin, levetiracetam and sodium valproate[117] are frequently proposed as alternatives in case of NIR to aromatic anticonvulsants/lamotrigine.

1. The TF suggests following DPT protocol with slowly increasing doses, as evaluated in the highest number of cases.[120] This

protocol determines the dose per body weight, with incremental dosages week after week (Table S1).

4.10 | Limitations

DPT can never exhibit 100% sensitivity or specificity; however, this is not required for making recommendations. Cofactors such as virus infection/reactivation, physical and psychological stress and simultaneous intake of other drugs are not reproduced during a DPT. It is difficult to standardize the method of DPT for drugs with different mechanisms and patterns of hypersensitivity. The dose used during provocation may also be insufficient to elicit a response in some cases leading to a risk of false negative testing.

5 | CONCLUSIONS

Drug provocation testing is an important tool when used after appropriate risk stratification in combination with the other investigations available in DH evaluation. We have provided practical guidance for selecting the best strategy for DPT with a range of different drug groups, balancing the best interest and safety of the patient with the constant focus on optimizing use of the available resources.

AUTHOR CONTRIBUTIONS

Annick Barbaud and Lene Heise Garvey (LHG) chaired the EAACI Drug Provocation Test Working Group. Annick Barbaud and Lene Heise Garvey led the discussions and drafted the general considerations section. Each author reviewed the literature, contributed to the general table A (supplement) and wrote his or her own section. Jose Julio Laguna, Anca Mirela Chiriac, Annick Barbaud, Lene Heise Garvey for beta-lactams, Maria Torres and Jean Christoph Caubet for NSAIDs, Knut Brockow for contrast agents, Kathrin Scherer Hofmeier and Josefina Cernadas for anti-infectives, Alessandra Arcolaci and Patrizia Bonadonna for PPIs and antihistamines 2, Lene Heise Garvey for perioperative anaphylaxis, Annick Barbaud for corticosteroids and anticonvulsants. All contributors took part in discussions and corrections during face-to-face and online meetings. All contributors approved the final version.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest in relation to this work.

DATA AVAILABILITY STATEMENT

There is no patient data in this paper. That is an analysis of the literature data.

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REFERENCES

1. Aberer W, Bircher A, Romano A, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. *Allergy*. 2003;58:854-863.
2. Audicana MT, Ortega N, Lobera T, et al. Spanish Society of Allergology and Clinical Immunology (SEAIC) vision of drug provocation tests. *J Investig Allergol Clin Immunol*. 2021;31(5):385-403.
3. Demoly P, Adkinson NF, Brockow K, et al. International consensus on drug allergy. *Allergy*. 2014;69(4):420-437.
4. Phillips EJ, Bigliardi P, Bircher AJ, et al. Controversies in drug allergy: testing for delayed reactions. *J Allergy Clin Immunol*. 2019;143:66-73.
5. Muraro A, Worm M, Alviani C, et al. EAACI guidelines: anaphylaxis (2021 update). *Allergy*. 2022;77(2):357-377.
6. Ramsey A, Mustafa SS, Holly AM, Staicu ML. Direct challenges to penicillin-based antibiotics in the inpatient setting. *J Allergy Clin Immunol Pract*. 2020;8:2294-2301.
7. Romano A, Atanaskovic-Markovic M, Barbaud A, et al. Towards a more precise diagnosis of hypersensitivity to beta-lactams—an EAACI position paper. *Allergy*. 2020;75:1300-1315.
8. Barbaud A, Castagna J, Soria A. Skin tests in the work-up of cutaneous adverse drug reactions: a review and update. *Contact Dermatitis*. 2022;86(5):344-356.
9. Fransson S, Mosbech HF, Elberling J, Kappel M, Garvey LH. Intradermal testing identifies 1 in 4 patients with nonimmediate penicillin allergy. *Int Arch Allergy Immunol*. 2021;182(9):827-834.
10. Brockow K, Garvey LH, Aberer W, et al. Skin test concentrations for systemically administered drugs—an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy*. 2013;68(6):702-712.
11. Mayorga C, Doña I, Perez-Inestrosa E, Fernández TD, Torres MJ. The value of in vitro tests to diminish drug challenges. *Int J Mol Sci*. 2017;18(6):1222.
12. Barbaud A, Weinborn M, Garvey LH, et al. Intradermal tests with drugs: an approach to standardization. *Front Med*. 2020;7:156.
13. van der Poorten MM, Walschot M, Faber M, et al. Reliability of early and late testing for suspected perioperative hypersensitivity. *J Allergy Clin Immunol Pract*. 2022;10(4):1057-1062.e2.
14. Soyer O, Sahiner UM, Sekerel BE. Pro and contra: provocation tests in drug hypersensitivity. *Int J Mol Sci*. 2017;18:1437.
15. Iammatteo M, Ferastraoaru D, Koransky R, et al. Identifying allergic drug reactions through placebo-controlled graded challenges. *J Allergy Clin Immunol Pract*. 2017;5(3):711-717.

16. Fransson S, Boel JB, Mosbech HF, Poulsen LK, Ruff S, Garvey LH. Safe de-labeling of patients at low risk of penicillin allergy in Denmark. *Int Arch Allergy Immunol*. 2022;183(6):640-650.
17. Iammatteo M, Lezmi G, Confino-Cohen R, Tucker M, Ben-Shoshan M, Caubet JC. Direct challenges for the evaluation of Beta-lactam allergy: evidence and conditions for not performing skin testing. *J Allergy Clin Immunol Pract*. 2021;9(8):2947-2956.
18. Barbaud A. Place of excipients in systemic drug allergy. *Immunol Allergy Clin North Am*. 2014;34(3):671-679.
19. Bruusgaard-Mouritsen MA, Nasser S, Garvey LH, Krantz MS, Stone CA Jr. Anaphylaxis to excipients in current clinical practice: evaluation and management. *Immunol Allergy Clin North Am*. 2022;42(2):239-267.
20. Garvey LH, Ebo DG, Mertes PM, et al. An EAACI position paper on the investigation of perioperative immediate hypersensitivity reactions. *Allergy*. 2019;74(10):1872-1884.
21. Pumphrey RS. Lessons for management of anaphylaxis from a study of fatal reactions. *Clin Exp Allergy*. 2000;30(8):1144-1150.
22. Garvey LH, Ebo DG, Krøigaard M, et al. The use of drug provocation testing in the investigation of suspected immediate perioperative allergic reactions: current status. *Br J Anaesth*. 2019;123(1):e126-e134.
23. Nohra D, Molinari N, Demoly P, Chiriac AM. Data-driven step doses for drug provocation tests to nonsteroidal anti-inflammatory drugs. *Allergy*. 2020;75(6):1423-1434.
24. Kepil Özdemir S, Bavbek S. Hypersensitivity reactions to proton-pump inhibitors: clinical presentation, diagnosis, and management. *Allergy Asthma Proc*. 2020;41(2):e37-e44.
25. Soyyiğit Ş, Aydın Ö, Yılmaz İ, et al. Evaluation of drug provocation test-related anxiety in patients with drug hypersensitivity. *Ann Allergy Asthma Immunol*. 2016;117:280-284.
26. Losappio LM, Cappai A, Arcolaci A, et al. Anxiety and depression effects during drug provocation test. *J Allergy Clin Immunol Pract*. 2018;6(5):1637-1641.
27. Lombardi C, Gargioni S, Canonica GW, Passalacqua G. The nocebo effect during oral challenge in subjects with adverse drug reactions. *Eur Ann Allergy Clin Immunol*. 2008;40(4):138-141.
28. Brockow K, Aberer W, Atanaskovic-Markovic M, et al. Drug allergy passport and other documentation for patients with drug hypersensitivity—an ENDA/EAACI Drug Allergy Interest Group position paper. *Allergy*. 2016;71(11):1533-1539.
29. Desroche T, Poreaux C, Waton J, Schmutz JL, Menetre S, Barbaud A. Can we allow a further intake of drugs poorly suspected as responsible in drug reaction with eosinophilia and systemic symptoms (DRESS)? A study of practice. *Clin Exp Allergy*. 2019;49:924-928.
30. Bermingham WH, Bhogal R, Arudi Nagarajan S, et al. Practical management of suspected hypersensitivity reactions to anti-tuberculosis drugs. *Clin Exp Allergy*. 2022;52(3):375-386.
31. Traineau H, Milpied B, Soria A, et al. In situ patch and repeated open application test for fixed drug eruption: a multicenter study. *J Allergy Clin Immunol Pract*. 2023. doi:10.1016/j.jaip.2023.10.021
32. de Las Vecillas Sánchez L, Alenazy LA, Garcia-Neuer M, Castells MC. Drug hypersensitivity and desensitizations: mechanisms and new approaches. *Int J Mol Sci*. 2017;18(6):1316.
33. Trubiano JA, Vogrin S, Chua KYL, et al. Development and validation of a penicillin allergy clinical decision rule. *JAMA Intern Med*. 2020;180(5):745-752.
34. Blumenthal KG, Huebner EM, Fu X, et al. Risk-based pathway for outpatient penicillin allergy evaluations. *J Allergy Clin Immunol Pract*. 2019;7(7):2411-2414.e1.
35. Blumenthal KG, Li Y, Hsu JT, et al. Outcomes from an inpatient beta-lactam allergy guideline across a large US health system. *Infect Control Hosp Epidemiol*. 2019;40(5):528-535.
36. Soria A, Autegarden E, Amsler E, et al. A clinical decision-making algorithm for penicillin allergy. *Ann Med*. 2017;49(8):710-717.
37. Collins C. The low risks and high rewards of penicillin allergy delabeling: an algorithm to expedite the evaluation. *J Pediatr*. 2019;212:216-223.
38. Devchand M, Kirkpatrick CMJ, Stevenson W, et al. Evaluation of a pharmacist-led penicillin allergy de-labelling ward round: a novel antimicrobial stewardship intervention. *J Antimicrob Chemother*. 2019;74(6):1725-1730.
39. Schrüfer P, Stoevesandt J, Trautmann A. Outcome of a de-labelling algorithm compared with results of penicillin (β-lactam) allergy testing. *Allergy Asthma Clin Immunol*. 2022;18(1):26.
40. Heng YK, Liew YCC, Kong YL, Lim YL. β-Lactam allergy testing and delabeling—experiences and lessons from Singapore. *Immun Inflamm Dis*. 2020;8(3):371-379.
41. Sneddon J, Cooper L, Ritchie N, et al. An algorithm for safe de-labelling of antibiotic allergy in adult hospital in-patients. *Clin Exp Allergy*. 2021;51(9):1229-1232.
42. Chiriac AM, Rerkpattanapipat T, Bousquet PJ, Molinari N, Demoly P. Optimal step doses for drug provocation tests to prove beta-lactam hypersensitivity. *Allergy*. 2017;72(4):552-561.
43. Prieto A, Muñoz C, Bogas G, et al. Single-dose prolonged drug provocation test, without previous skin testing, is safe for diagnosing children with mild non-immediate reactions to beta-lactams. *Allergy*. 2021;76(8):2544-2554.
44. Caubet JC. Management of children with a suspicion of immediate drug hypersensitivity. *Allergy*. 2021;76(3):940-941.
45. Gomes ER, Brockow K, Kuyucu S, et al. Drug hypersensitivity in children: report from the pediatric task force of the EAACI Drug Allergy Interest Group. *Allergy*. 2016;71(2):149-161.
46. Li J, Cvetanovski V, Fernando S. Single-step direct drug provocation testing is safe for delabelling selected non-low-risk penicillin allergy labels. *Ann Allergy Asthma Immunol*. 2021;127(2):232-235.
47. Kuruvilla M, Shih J, Patel K, Scanlon N. Direct oral amoxicillin challenge without preliminary skin testing in adult patients with allergy and at low risk with reported penicillin allergy. *Allergy Asthma Proc*. 2019;40(1):57-61.
48. Trubiano JA, Vogrin S, Copaescu A, et al. Direct oral penicillin challenge for penicillin allergy delabeling as a health services intervention: a multicenter cohort study. *Allergy*. 2022;77(3):1038-1042.
49. Fransson S, Mosbech H, Kappel M, et al. The importance of prolonged provocation in drug allergy—results from a Danish Allergy Clinic. *J Allergy Clin Immunol Pract*. 2017;5(5):1394-1401.
50. Van Gasse AL, Ebo DG, Chiriac AM, et al. The limited value of prolonged drug challenges in nonimmediate amoxicillin (clavulanic acid) hypersensitivity. *J Allergy Clin Immunol Pract*. 2019;7:2225-2229.
51. Hjortlund J, Mortz CG, Skov PS, et al. One-week oral challenge with penicillin in diagnosis of penicillin allergy. *Acta Derm Venereol*. 2012;92(3):307-312.
52. García Rodríguez R, Moreno Lozano L, Extremera Ortega A, Borja Segade J, Galindo Bonilla P, Gómez TE. Provocation tests in non-immediate hypersensitivity reactions to β-lactam antibiotics in children: are extended challenges needed? *J Allergy Clin Immunol Pract*. 2019;7(1):265-269.
53. Regateiro FS, Rezende I, Pinto N, Abreu C, Carreiro-Martins P, Gomes ER. Short and extended provocation tests have similar negative predictive value in non-immediate hypersensitivity to beta-lactams in children. *Allergol Immunopathol*. 2019;47(5):477-483.
54. Doña I, Guidolin L, Bogas G, et al. Resensitization in suspected penicillin allergy. *Allergy*. 2023;78(1):214-224.
55. Süleyman A, Yücel E, Tamay ZÜ, Güler N. Evaluation of suspected macrolide allergies in children. *Turk Arch Pediatr*. 2022;57(1):81-86.
56. Ünal D, Demir S, Gelincik A, et al. Diagnostic value of oral challenge testing in the diagnosis of macrolide hypersensitivity. *J Allergy Clin Immunol Pract*. 2018;6(2):521-527.

57. Doña I, Pérez-Sánchez N, Salas M, et al. Clinical characterization and diagnostic approaches for patients reporting hypersensitivity reactions to quinolones. *J Allergy Clin Immunol Pract*. 2020;8(8):2707-2714.
58. Demir S, Gelincik A, Akdeniz N, et al. Usefulness of in vivo and in vitro diagnostic tests in the diagnosis of hypersensitivity reactions to quinolones and in the evaluation of cross-reactivity: a comprehensive study including the latest quinolone gemifloxacin. *Allergy Asthma Immunol Res*. 2017;9(4):347-359.
59. Krantz MS, Stone CA Jr, Yu R, Adams SN, Phillips EJ. Criteria for intradermal skin testing and oral challenge in patients labeled as fluoroquinolone allergic. *J Allergy Clin Immunol Pract*. 2021;9(2):1024-1028.
60. Krantz MS, Stone CA, Abreo A, Phillips AJ. Oral challenge with trimethoprim-sulfamethoxazole in patient with "sulfa" antibiotic allergy. *J Allergy Clin Immunol Pract*. 2020;8(2):757-760.
61. García-Rubio I, Martínez-Cócera C, Santos Magadán S, Rodríguez-Jiménez B, Vázquez-Cortés S. Hypersensitivity reactions to metronidazole. *Allergol Immunopathol*. 2006;34(2):70-72.
62. Maciag MC, Ward SL, O'Connell AE, Broyles AD. Hypersensitivity to tetracyclines: skin testing, graded challenge, and desensitization regimens. *Ann Allergy Asthma Immunol*. 2020;124(6):589-593.
63. Ebo DG, Mertens C, Braes M, Mennes I, Bridts CH, Sabato V. Clindamycin anaphylaxis confirmed by in vivo and in vitro testing. *J Allergy Clin Immunol Pract*. 2019;7(1):331-333.
64. Perrin-Lamarre A, Petitpain N, Trechot P, Cuny JF, Schmutz JL, Barbaud A. Glycopeptide-induced cutaneous adverse reaction: results of an immunoallergic investigation in eight patients. *Ann Dermatol Venereol*. 2010;137(2):101-105.
65. Kayode OS, Rutkowski K, Haque R, Till SJ, Siew LQC. Teicoplanin hypersensitivity in perioperative anaphylaxis. *J Allergy Clin Immunol Pract*. 2020;8(6):2110-2113.
66. Christiansen IS, Pedersen P, Krøigaard M, Mosbech H, Garvey LH. Anaphylaxis to intravenous gentamicin with suspected sensitization through gentamicin-loaded bone cement. *J Allergy Clin Immunol Pract*. 2016;4(6):1258-1259.
67. Sharma R, Verma G, Tegta G, Sood S, Renu R, Gupta R. Spectrum of cutaneous adverse drug reactions to anti-tubercular drugs and safetherapy after re-challenge—a retrospective study. *Indian Dermatol Online J*. 2017;10(4):481-485.
68. Ban G-Y, Jeong Y-J, Lee S-H, et al. Efficacy and tolerability of desensitization in the treatment of delayed drug hypersensitivities to anti-tuberculosis medications. *Respir Med*. 2019;147:44-50.
69. Quiralte J, Blanco C, Castillo R, Delgado J, Carrillo T. Intolerance to nonsteroidal antiinflammatory drugs: results of controlled drug challenges in 98 patients. *J Allergy Clin Immunol*. 1996;98(3):678-685.
70. Asero R. Use of ketoprofen oral challenges to detect cross-reactors among patients with a history of aspirin-induced urticaria. *Ann Allergy Asthma Immunol*. 2006;97(2):187-189.
71. Doña I, Blanca-López N, Cornejo-García JA, et al. Characteristics of subjects experiencing hypersensitivity to non-steroidal anti-inflammatory drugs: patterns of response. *Clin Exp Allergy*. 2011;41(1):86-95.
72. Viola M, Rumi G, Valluzzi RL, Gaeta F, Caruso C, Romano A. Assessing potential determinants of positive provocation tests in subjects with NSAID hypersensitivity. *Clin Exp Allergy*. 2011;41(1):96-103.
73. Bavbek S, Yilmaz I, Celik G, et al. Prevalence of aspirin-exacerbated respiratory disease in patients with asthma in Turkey: a cross-sectional survey. *Allergol Immunopathol*. 2012;40(4):225-230.
74. Ariza A, Fernandez TD, Doña I, et al. Basophil activation after nonsteroidal anti-inflammatory drugs stimulation in patients with immediate hypersensitivity reactions to these drugs. *Cytometry A*. 2014;85(5):400-407.
75. Doña I, Jurado-Escobar R, Perkins JR, et al. Eicosanoid mediator profiles in different phenotypes of nonsteroidal anti-inflammatory drug-induced urticaria. *Allergy*. 2019;74(6):1135-1144.
76. Li L, Bensko J, Buchheit K, Saff RR, Laidlaw TM. Safety, outcomes, and recommendations for two-step outpatient nonsteroidal anti-inflammatory drug challenges. *J Allergy Clin Immunol Pract*. 2022;10(5):1286-1292.
77. Nohra D, Schrijvers R, Touati N, et al. Risk factors for positive paracetamol drug provocation testing and procedure optimization. *J Allergy Clin Immunol Pract*. 2019;7(6):2045-2048.
78. Kepil Özdemir S, Öner Erkekol F, Ünal D, et al. Management of hypersensitivity reactions to proton pump inhibitors: a retrospective experience. *Int Arch Allergy Immunol*. 2016;171(1):54-60.
79. Bonadonna P, Lombardo C, Bortolami O, et al. Hypersensitivity to proton pump inhibitors: diagnostic accuracy of skin tests compared to oral provocation test. *J Allergy Clin Immunol*. 2012;130(2):547-549.
80. Sánchez-Morillas L, Rojas Pérez-Ezquerra P, González Mendiola R, Gómez-Tembleque Ubeda P, Santos Alvarez A, Laguna-Martínez JJ. Eleven cases of omeprazole hypersensitivity: diagnosis and study of cross-reactivity. *J Investig Allergol Clin Immunol*. 2014;24(2):130-132.
81. Barbaud A, Romano A. Skin testing approaches for immediate and delayed hypersensitivity reactions. *Immunol Allergy Clin North Am*. 2022;42(2):307-322.
82. Lin CY, Wang CW, Hui CR, et al. Delayed-type hypersensitivity reactions induced by proton pump inhibitors: a clinical and in vitro T-cell reactivity study. *Allergy*. 2018;73(1):221-229.
83. Makris M, Aggelides X, Chliva C, Katoulis A, Papamichael K, Tiligada E. High baseline blood histamine levels and lack of cross-reactivity in a patient with ranitidine-induced anaphylaxis. *J Investig Allergol Clin Immunol*. 2014;24(5):361-363.
84. Park KH, Pai J, Song DG, et al. Ranitidine-induced anaphylaxis: clinical features, cross-reactivity, and skin testing. *Clin Exp Allergy*. 2016;46(4):631-639.
85. Torres MJ, Trautmann A, Böhm I, et al. Practice parameters for diagnosing and managing iodinated contrast media hypersensitivity. *Allergy*. 2021;76(5):1325-1339.
86. Torres MJ, Gomez F, Doña I, et al. Diagnostic evaluation of patients with nonimmediate cutaneous hypersensitivity reactions to iodinated contrast media. *Allergy*. 2012;67(7):929-935.
87. Salas M, Gomez F, Fernandez TD, et al. Diagnosis of immediate hypersensitivity reactions to radiocontrast media. *Allergy*. 2013;68(9):1203-1206.
88. Lerondeau B, Trechot P, Waton J, et al. Analysis of cross-reactivity among radiocontrast media in 97 hypersensitivity reactions. *J Allergy Clin Immunol*. 2016;137(2):633-635.
89. Morales-Cabeza C, Roa-Medellín D, Torrado I, et al. Immediate reactions to iodinated contrast media. *Ann Allergy Asthma Immunol*. 2017;119(6):553-557.
90. Rosado Ingelmo A, Doña Diaz I, Cabañas Moreno R, et al. Clinical practice guidelines for diagnosis and management of hypersensitivity reactions to contrast media. *J Investig Allergol Clin Immunol*. 2016;26(3):144-155.
91. Schrijvers R, Breynaert C, Ahmedali Y, Bourrain JL, Demoly P, Chiriac AM. Skin testing for suspected iodinated contrast media hypersensitivity. *J Allergy Clin Immunol Pract*. 2018;6(4):1246-1254.
92. Soria A, Masson N, Vial-Dupuy A, et al. Allergological workup with half-dose challenge in iodinated contrast media hypersensitivity. *Allergy*. 2019;74(2):414-417.
93. Trautmann A, Brockow K, Behle V, Stoevesandt J. Radiocontrast media hypersensitivity: skin testing differentiates allergy from nonallergic reactions and identifies a safe alternative as proven by intravenous provocation. *J Allergy Clin Immunol Pract*. 2019;7(7):2218-2224.

94. Gracia-Bara MT, Moreno E, Laffond E, et al. Tolerability of iobitridol in patients with non-immediate hypersensitivity reactions to iodinated contrast media. *Allergy*. 2019;74(1):195-197.
95. Meucci E, Radice A, Fassio F, et al. Diagnostic approach to hypersensitivity reactions to iodinated contrast media: a single-center experience on 98 patients. *Eur Ann Allergy Clin Immunol*. 2020;52(5):220-229.
96. Doña I, Bogas G, Salas M, et al. Hypersensitivity reactions to multiple iodinated contrast media. *Front Pharmacol*. 2020;11:575437.
97. Vega F, Múgica MV, Bazire R, et al. Adverse reactions to iodinated contrast media: safety of a study protocol that includes fast full-dose parenteral challenge tests searching for an alternative contrast media. *Clin Exp Allergy*. 2020;50(2):271-274.
98. Sánchez-Borges M, Aberer W, Brockow K, et al. Controversies in drug allergy: radiographic contrast media. *J Allergy Clin Immunol Pract*. 2019;7(1):61-65.
99. Kwon OY, Lee JH, Park SY, et al. Novel strategy for the prevention of recurrent hypersensitivity reactions to radiocontrast media based on skin testing. *J Allergy Clin Immunol Pract*. 2019;7(8):2707-2713.
100. Seta V, Gaouar H, Badaoui A, Francès C, Barbaud A, Soria A. Low-dose provocation and skin tests in patients with hypersensitivity to gadolinium-based contrast agents. *Clin Exp Allergy*. 2019;49(5):724-728.
101. Madrigal-Burgaleta R, Bernal-Rubio L, Berges-Gimeno MP, Carpio-Escalona LV, Gehlhaar P, Alvarez-Cuesta E. A large single-hospital experience using drug provocation testing and rapid drug desensitization in hypersensitivity to antineoplastic and biological agents. *J Allergy Clin Immunol Pract*. 2019;7(2):618-632.
102. Pagani M, Bavbek S, Alvarez-Cuesta E, et al. Hypersensitivity reactions to chemotherapy: an EAACI position paper. *Allergy*. 2022;77(2):388-403.
103. Bavbek S, Pagani M, Alvarez-Cuesta E, et al. Hypersensitivity reactions to biologicals: an EAACI position paper. *Allergy*. 2022;77(1):39-54.
104. Picard M, Pur L, Caiado J, et al. Risk stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions. *J Allergy Clin Immunol*. 2016;137(4):1154-1164.
105. Tsao LR, Young FD, Otani IM, Castells MC. Hypersensitivity reactions to platinum agents and taxanes. *Clin Rev Allergy Immunol*. 2022;62(3):432-448.
106. Madrigal-Burgaleta R, Vazquez-Revuelta P, Marti-Garrido J, Lleonart-Bellfill R, Ali FR, Alvarez-Cuesta E. Medical algorithm: diagnosis and treatment of hypersensitivity reactions to cancer chemotherapy. *Allergy*. 2021;76(8):2636-2640.
107. Laguna JJ, Archilla J, Doña I, et al. Practical guidelines for perioperative hypersensitivity reactions. *J Investig Allergol Clin Immunol*. 2018;28(4):216-232.
108. Li PH, Ue KL, Wagner A, Rutkowski R, Rutkowski K. Opioid hypersensitivity: predictors of allergy and role of drug provocation testing. *J Allergy Clin Immunol Pract*. 2017;5(6):1601-1606.
109. Kalangara J, Potru S, Kuruvilla M. Clinical manifestations and diagnostic evaluation of opioid allergy labels—a review. *J Pain Palliat Care Pharmacother*. 2019;33(3–4):131-140.
110. Nasser SM, Ewan PW. Opiate-sensitivity: clinical characteristics and the role of skin prick testing. *Clin Exp Allergy*. 2001;31:1014-1020.
111. Trautmann A, Goebeler M, Stoevesandt J. Twenty years' experience with anaphylaxis-like reactions to local anesthetics: genuine allergy is rare. *J Allergy Clin Immunol Pract*. 2018;6(6):2051-2058.
112. Kvisselgaard A, Mosbech H, Fransson S, Garvey LH. Risk of immediate type allergy to local anaesthetics is over-estimated—results from 5 years of provocation testing in a Danish Allergy Clinic. *J Allergy Clin Immunol Pract*. 2018;6:1217-1223.
113. Baeck M, Chemelle JA, Goossens A, Nicolas JF, Terreux R. Corticosteroid cross-reactivity: clinical and molecular modelling tools. *Allergy*. 2011;66:1367-1374.
114. Barbaud A, Waton J. Systemic allergy to corticosteroids: clinical features and cross reactivity. *Curr Pharm Des*. 2016;22(45):6825-6831.
115. Li PH, Wagner A, Thomas I, Watts TJ, Rutkowski R, Rutkowski K. Steroid allergy: clinical features and the importance of excipient testing in a diagnostic algorithm. *J Allergy Clin Immunol Pract*. 2018;6(5):1655-1661.
116. Padial A, Posadas S, Alvarez J, et al. Non immediate reactions to systemic corticosteroids suggest an immunological mechanism. *Allergy*. 2005;60:665-670.
117. Fowler T, Bansal AS, Lozsádi D. Risks and management of antiepileptic drug induced skin reactions in the adult out-patient setting. *Seizure*. 2019;72:61-70.
118. Mori F, Blanca-Lopez N, Caubet JC, et al. Delayed hypersensitivity to antiepileptic drugs in children. *Pediatr Allergy Immunol*. 2021;32(3):425-436.
119. Naisbitt DJ, Britschgi M, Wong G, et al. Hypersensitivity reactions to carbamazepine: characterization of the specificity, phenotype, and cytokine profile of drug-specific T cell clones. *Mol Pharmacol*. 2003;63(3):732-741.
120. Atanasković-Marković M, Janković J, Tmušić V, et al. Hypersensitivity reactions to antiepileptic drugs in children. *Pediatr Allergy Immunol*. 2019;30(5):547-552.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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