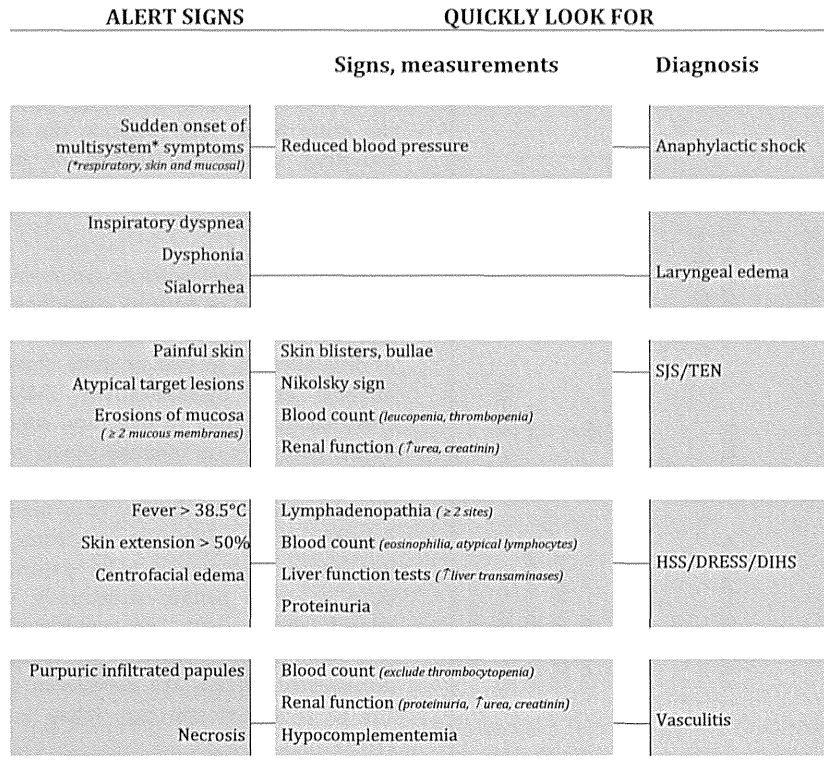

Figure 2 Clinical and biological danger signs suggesting severe cutaneous and/or systemic reactions (created using data from (62)).

Diagnosis

The diagnosis of DHRs requires knowledge of the scientific literature with access to Medline searches and to the Committee on Safety of Medicine and Embase Reports for the more recently introduced drugs. The lack of case studies involving a particular compound does not mean that it cannot induce a DHR, but for a widely used drug, it renders DHRs much less likely. The diagnosis is indeed based on history, on clinical manifestations, and if possible, on *in vivo* tests and some *in vitro* biological tests (Fig. 3) (78). However, only a few clinical and biological tools are available and fully validated. Moreover, a definitive diagnosis of such a reaction is preferred in order to institute proper preventive measures (Box 3).

Evaluation of the clinical history

Clinical history must be carefully obtained and should include the symptomatology (whether compatible with a DHR), the chronology of the symptoms (previous exposure, delay between the last dose and the onset of symptoms, effect of stopping treatment), other medications taken (both at the time of the reaction and other drugs of the same class taken since), and the medical background of the patient (any suggestion of a previous allergy, whether associated with medication or not, or of a medical condition, such as chronic urticaria/chronic rhinosinusitis, that can be aggravated by the intake of certain drugs such as aspirin and noncycloxygenase two selective NSAIDs). Data should ideally be recorded in a uniform format, and in order to harmonize the DHR diagnostic procedures, members of EAACI-DAIG/ENDA have developed a questionnaire (11) available in many different languages (Appendix S1 in the online Supporting Information). Diagnosis is more difficult when patients are not seen during the symptomatic phase, in which case photographs are helpful. When patients are seen during the reaction, the suspected drugs should be stopped after a benefit/risk balance analysis, especially if danger/severity signs are present (Fig. 2) (62).

A large number of reactions are presumed to be drug related and allergic in nature, but closer examination often reveals that they are not (3, 5). The history is often not reliable because different drugs are frequently taken simultaneously and each of them can account for the symptoms, although often with very different *a priori* probabilities. History can also be imprecise in many cases. Finally, the clinical picture of DHRs is very heterogeneous, mirroring many distinct pathophysiological events (Table 2). Thus, for the diagnosis of DHR, many healthcare professionals rely on history and various reference manuals. They do not attempt to prove the relationship between the drug intake and the symptoms or to clarify the underlying

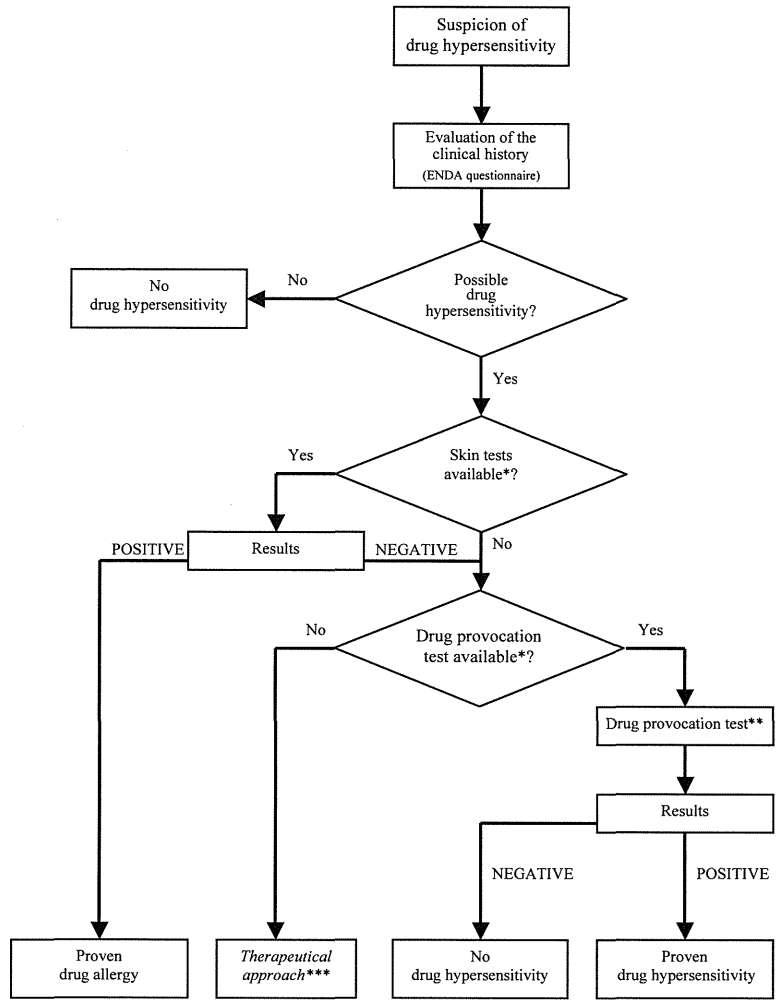

Figure 3 Flow chart when assessing DHRs (adapted from (78) with permission). *Currently available biological tests to diagnose drug allergy lack sensitivity. **In the absence of contraindications (Box 6). ***If no alternative is available (e.g., NMBA, chemotherapeutica drugs), readministration of the drug is allowed under close surveillance, considering premedication and/or desensitization.

pathomechanism of the reaction. Such practice leads to a misunderstanding of the epidemiology and the pathophysiology of this highly relevant field. Members of the panel have listed situations in order to determine when to test and when not to test in suspected DHR (Boxes 4 and 5). An accurate diagnosis of DHRs allows implementation of the best measures required for prevention and treatment. For universal drugs such as β-lactams, NSAIDs, local anesthetics, simply avoiding the drug is not sufficient (Box 4). This procedure could lead to the contraindication of drugs which do not necessarily give rise to reactions and which are widely used. Besides, a false diagnosis can lead to a fake sense of security if other possible causes of serious reactions are not explored and excluded. However, this is a valid option until a specialist consultation can be scheduled.

Box 3: Key points regarding DHR diagnosis

1. A definitive diagnosis of a DHR is in many cases required in order to institute proper preventive measures.
2. Misclassification based on the DHR history alone may have consequences on individual treatment choices and be more detrimental for the patients than a complete drug allergy workup.
3. The clinical tools allowing a definitive diagnosis include a thorough clinical history, standardized skin tests, reliable *in vitro* tests, and drug provocation tests.
4. When properly performed in specialized centers, a reliable diagnosis is often possible and safe alternative medication can be administered.
5. Screening subjects without a prior history of allergic drug reactions is not recommended.

Box 4: DHR workup: When to evaluate?

1 When there is a history of prior DHR and the drug is required without an equally effective, structurally unrelated alternative, and if the risk/possible benefit ratio is positive:
   - **a** For the majority of patients with β-lactam, NSAIDs, local anesthetics DHRs.
   - **b** For others when drugs are required (depending on an individual medical needs).
2 When there is a history of prior severe DHR for other drugs (the best way to protect the patient is to find the culprit agents).

Box 5: DHR workup: When not to evaluate?

1 Cases with no drug allergy causality:
   - **a** Noncompatible symptomatology
   - **b** Noncompatible chronology
   - **c** Drug taken since with no reaction
   - **d** Reaction without having taken the drug
   - **e** Alternative diagnosis (e.g., herpesvirus eruption, chronic urticaria)
2 For drug provocation, every time the reaction was too severe: noncontrollable reaction and severe life-threatening reactions (Box 6)

The specific allergy workup should be carried out 4–6 weeks after the complete resolution of all clinical symptoms and signs (R2, Evidence D). How early testing can be made without results being falsely negative is unknown. On the other hand, after a time interval of more than 6–12 months, some drug tests may already have turned negative. These could be false-negative results (or true negative) depending on the results of the subsequent drug provocation test. According to the clinical presentations, a hypothesis on pathogenesis should be generated (Table 2) in order to select appropriate testing procedures (12, 62).

Pharmacovigilance algorithms

Pharmacovigilance algorithms for diagnosis are based principally on the clinical history (79); they are rarely specific for DHRs (80). They rarely produce a firm diagnosis of DHRs, and allergy testing is often necessary (79). Indeed, the symptoms are often suggestive, but not necessarily definitive in diagnosing DHR. The effect of discontinuation of the drug is not always conclusive (e.g., rebounds of urticaria after drug withdrawal is possible for a few hours) and no biological examination is reliable and specific. Often there is a lack of accurate information (imprecise chronology, exact name of drug or of corrective treatment not recalled by the patient), making drug causality assessment difficult to ascertain.

Skin tests

Skin tests are the most readily available means for confirming or excluding sensitization (22). Their diagnostic value has not been fully evaluated for all drugs, and over the past decades, experience among different centers has rarely been exchanged in a systematic manner (22). These tests should follow standard procedures and should be performed by trained staff (6, 12). They should be performed 4–6 weeks after the reaction (R2, Evidence D). Skin tests have to be applied depending on the suspected pathomechanism of the DHR.

Skin prick tests and intradermal tests are particularly important for reactive haptens in order to demonstrate an IgE-dependent mechanism (62). Thus, for immediate DHRs, the prick test is recommended for initial screening due to its simplicity, rapidity, low cost, and high specificity. Intradermal tests (12) are undertaken when skin prick tests are negative. Compared to skin prick tests, they provide an enhanced sensitivity for drug-specific IgE (12). They should be performed with the intravenously injectable form of the drug whenever possible (22). Their sensitivity and predictive values vary, depending on the culprit drug and the clinical presentation. They appear to be 'good' for immediate DHRs to β-lactam antibiotics, NMBA, platin salts, and heparins, but moderate to low for most other drugs (R3, Evidence B) (22).

In order to demonstrate a T-cell-dependent mechanism for nonimmediate DHRs (manifesting by cutaneous symptoms such as a maculopapular exanthema occurring within hours after the last drug intake), patch tests and/or late-reading intradermal tests should be performed (15, 62). Unfortunately, apart from allergic reactions to several antibiotics and a few other drugs (81), for most drug allergens, standardized and validated test concentrations and vehicles have not been studied or are disputed in the literature. Sometimes the drug is not available in an adequately reactive form, generally because it is a metabolic derivative which is immunogenic and not the parent drug. In such cases, provocation tests are required to confirm the diagnosis. Available data have been summarized by EAACI-DAIG/ENDA experts (22).

Testing subjects without a prior history of an allergic drug reaction is not supported by available studies and therefore not recommended by any of the societies, in particular in preoperative settings (20).

While there is general agreement among guidelines on the importance of skin testing in the drug allergy workup, some discrepancies arise. The authors of the US Practice Parameters (6) consider that immediate DHRs to iodinated radiocontrast media (RCM) are all nonallergic (described as 'anaphylactoid') in nature and do not include skin testing in the management of a patient having experienced a previous DHR to iodinated RCM. This position is challenged by the multicenter study of EAACI-DAIG/ENDA (82), thus encouraging further studies (R4, Evidence C).

Provocation tests

A drug provocation test (DPT), also referred to as drug challenge, graded challenge, or test dosing, is the gold standard for the identification of the drug eliciting a DHR (R5, Evidence C). Whereas all the guidelines agree that the DPT

comes at the end of the stepwise approach in drug allergy (due to its inherent risks), it holds a slightly different meaning, depending on different guidelines. The authors of the US Practice Parameters (6) consider that the procedure is intended for patients who, after a full evaluation, are unlikely to be allergic to the given drug, that is, DPT performed to demonstrate tolerance to a less likely eliciting drug. The BSACI (8) guideline considers the primary aim of a DPT as a means to exclude DHR, but it can also be used to confirm a diagnosis. The EAACI-DAIG/ENDA guideline (13) addresses its role as a gold standard to establish or exclude the diagnosis of DHRs, but agrees that in some clinical practice situations, it might be more useful to look for safe alternatives instead of testing with a drug which was the definitive cause of the problem. It also mentions the altruistic and scientific value of the DPT (i.e., other patients might benefit from the obtained knowledge), but in these cases (and not in routine practice), approval by an ethical committee is mandatory.

The DPT is independent of the pathogenesis and consequently cannot differentiate between allergic from nonallergic DHRs. It takes individual factors such as the metabolism and genetic disposition of an individual into account. DPTs have the highest sensitivity, but should only be performed under the most rigorous surveillance conditions (Box 6). They are therefore usually restricted to certain specialist centers in which equipment, supplies, and personnel are present to manage serious reactions, and that personnel are well trained and experienced in performing this procedure in properly selected patients (13).

Box 6: Precautions and contraindications of performing DPTs

1. DPTs are contraindicated in noncontrollable and/or severe life-threatening DHRs:
   - **a** Severe cutaneous reactions such as SJS, TEN, DRESS, vasculitis, AGEP
   - **b** Systemic reactions such as DRESS, any internal organ involvement, hematological reactions
   - **c** Anaphylaxis may be tested after risk/benefit analysis
2. DPTs are not indicated when:
   - **a** The offending drug is unlikely to be needed and several structurally unrelated alternatives exist
   - **b** Severe concurrent illness or pregnancy (unless the drug is essential for the concurrent illness or required during pregnancy or delivery)
3. DPTs should be performed under the highest safety conditions:
   - **a** Trained staff: aware of the tests, ready to identify early signs of a positive reaction, and ready to manage a life-threatening reaction
   - **b** With emergency resuscitative equipment available

These tests are particularly required for nonsteroidal anti-inflammatory drugs (23), local anesthetics, antibiotics other than β-lactams, and β-lactams when skin tests are negative. They should be performed after a certain time interval following the DHR (at least 1 month) (R2, Evidence D) using, whenever possible, the same drug as in the initial reaction (13). Sometimes, when the clinical history has a favorable positive predictive value, performing DPT directly with an alternative drug seems more judicious (e.g., a cycloxygenase-2 antagonist is typically tolerated uneventfully in the case of NSAID cross-reactors). Some authors evoke the option of prolonged DPTs (performed at home) in patients (children especially) with nonimmediate and nonsevere reactions (53, 83–85), sometimes without previous skin tests (53, 85). Recommendations have not yet echoed this strategy.

The route of administration depends on the suspected drug, which should in principle be administered in the same way as it was given when the initial reaction occurred. However, all the guidelines agree that the oral route is preferred whenever possible (R6, Evidence D). The precise challenge procedure varies a great deal from one team to another, and guidelines for the performance of DPTs have been proposed (13). A summary of DPT protocols has been reported in retrospective studies of more than one thousand consecutive patients (5, 85).

There is general consensus regarding the contraindications of DPT (see Box 6), with respect to the severity of the initial reaction and the availability of immediate treatment allowing complete and fast recovery (R7, Evidence D). The US Practice Parameters (6) state that rare exceptions to this may exist, such as treatment of a life-threatening illness, in which case the benefit of treatment outweighs the risk of a potentially life-threatening reaction. Arguments against a DPT would be if the offending drug is infrequently used and several alternatives exist. BSACI (8) and EAACI-DAIG/ENDA guidelines (13) mention that severe concurrent illness and pregnancy are generally considered as contraindications to DPT, unless the drug is essential for the concurrent illness (i.e., neurosyphilis and penicillin therapy, although desensitization may be considered first) or required during pregnancy or delivery (i.e., local anesthetics although it is not a classical DPT because subcutaneous injections are followed by a full dose of epidural anesthetic).

Despite the advantage of DPT over all the other test procedures, it has its limitations. First, the patient does not like to be re-exposed to a drug, which he or she considers harmful. Secondly, severe reactions are not amenable to DPTs (Box 6). Finally, a negative test does not prove tolerance to the drug in the future, but rather that there is no DHR at the time of the challenge and to the doses challenged. Nevertheless, a high negative predictive value (NPV) of β-lactam DPT of 94–98% was found in large studies involving both children and adults (86, 87), and most of the reactions reported by patients were both mild and nonimmediate reactions. Similarly, the NPV of DPT with NSAIDs also appears to be high (over 96%) whatever the NSAID (the one negatively tested or an alternative), and none of the false-negative patients described a life-threatening reaction (88). Desensitization by testing, as cause of false-negative DPT, is mentioned by the EAACI-DAIG/ENDA guideline (13) and the US Practice Parameters (6), but no reference to the existing literature is made. Resensitization by testing is addressed by EAACI-DAIG/ENDA (13) and BSACI (8) guidelines, with

respect to β-lactam allergy. Several studies have observed re-sensitization (i.e., a conversion to skin test positivity) after a negative DPT (followed by full therapeutic courses), with a frequency ranging from 0.9% (89) to 27.9% (90). Although this view is not mentioned in all guidelines and is not widely accepted, one approach might be to retest (2–4 weeks later) the patients who suffered severe immediate reactions and who displayed negative results at the first evaluation, which included a DPT (18) (R8, Evidence D).

Biological tests

It would be highly advantageous to have discriminating biological tests available in order to establish the nature of the culprit agent. This would be helpful particularly for the patient receiving several drugs simultaneously and for severe life-threatening DHRs when skin tests are negative or not possible, and DPT contraindicated (Box 6). However, with some exceptions (e.g., major and minor determinants of penicillin G), the currently available biological methods to diagnose drug allergy lack sensitivity, although they are normally considered to be quite specific (>90%). There are no established methods to predict the immunogenic potential of a drug. It should also be remembered that the results need to be interpreted with caution. A negative test does not exclude the imputability of the drug, while a positive result shows a sensitivity to the drug, but does not reliably confirm its causality (R9, Evidence C).

In vitro assay for drug-specific IgE is not available for many allergenic drugs and, conversely, is offered for many drugs without evidence of validated assays. The demonstration of isolated drug-specific IgE (to penicillins (91), NMBA (92), chymopapain, or tetanus toxoid, for example) does not establish the diagnosis of a drug allergy. However, in conjunction with clinical findings (e.g., typical severe symptoms of rapid onset), an IgE-dependent mechanism can be assumed (particularly if the skin tests to the drug are also positive) (18, 91). Thus, EAACI-DAIG/ENDA advises that skin tests to antibiotics should be performed after IgE testing in severe immediate reactions (22). *In vitro* cross-reactivities between several drugs using quantitative inhibition may also be explored, knowing that its predicted clinical outcome is not fully validated (93). The absence of drug-specific circulating IgE does not rule out a diagnosis of immediate drug allergy (R9, Evidence C). Measurement of drug-specific IgM or IgG is of interest only in cases of drug-induced cytopenia, type III DHRs to vaccines or allergies to dextrans. However, the sensitivity of these tests is unknown and they are not widely available. *In vitro* histamine release from whole blood in the presence of the drug correlates well with skin tests and specific IgE for NMBA, but is not reliable for many other drugs (94). Moreover, it is costly and requires a high level of technical expertise. The usefulness of measuring sulfidopeptide leukotrienes produced *in vitro* by isolated peripheral blood leukocytes after allergenic drug stimulation still requires further validation in both IgE-dependent allergies and non-IgE-dependent DHRs (95). In cases of acute clinical reactions, blood measurements of histamine or tryptase may confirm an involvement of basophils and mast cells whatever the cause of the degranulation (20, 96). Although tests for histamine are not widely commercially available, the test for tryptase is CAP FEIA (20). Basophil activation tests with flow cytometric reading hold promise and are currently undergoing validation for certain drugs (97–99).

For drug-induced type II and III allergic reactions, the following tests can be performed in some centers: Coombs' test, *in vitro* hemolysis test, determination of complement factors and circulating immune complexes. Assays involving T cells (lymphocyte transformation/activation tests) remain the domain of only a few laboratories with experience in DHRs, whereas results from commercial laboratories are generally not reliable (100). Searching for genetic markers may prove helpful, as several strong genetic associations between the expression of a particular HLA allele and the susceptibility to specific forms of DHRs have been recently discovered (Table 3) (50). For the drug abacavir, an association between B*5701 expression and DRESS has prompted the development of predictive testing strategies (47) and labeling changes to drug information sheets. The same is now true for the drug carbamazepine in Han Chinese and the allele B*1502 (101). The positive predictive value of the polymorphisms found so far varies widely (Table 3) and may not always lead to the simple and very successful predictive strategy of abacavir and B*5701 (R10, Evidence A).

Principles of drug allergy management

Acute drug reactions

Anaphylaxis must be treated promptly and appropriately (8), (102, 103), and all suspected drugs must be stopped (102, 104).

When patients experiencing nonanaphylactic reactions are examined during a reaction, the suspected drugs should be stopped if the risks of continuing the administration of the drug outweigh the benefits, and always if danger/severity signs are present (Fig. 2) (62). Indeed, during the acute phase of a severe delayed DHR, the putative drug as well as all 'less necessary' medication should be stopped with no delay in order to improve the prognosis (105).

Supportive treatment for delayed DHRs is not specifically covered by current drug allergy guidelines, but can be found in general reviews (58, 102, 106).

Individual preventive measures

A definitive diagnosis of DHRs allows more targeted preventive measures. Whatever the intensity of the clinical reaction, a state of hypersensitivity is shown toward the particular drug, with the possibility of a more serious reaction in the future. Individual measures include the issue of a written documentation specifying the culprit agent(s), the insertion of the allergy in the tab of the electronic medical record, the drawing up of a list of drugs to avoid, as well as a list of possible alternatives. The lists are only indicative and should be frequently updated (R11, Evidence D). The search for alternatives may require DPTs in a hospital setting when the alternatives belong to the same drug class (R12, Evidence C). The questioning (to elicit

any history of drug allergy) of every patient by every clinician prior to issuing a prescription is essential from both a medical and a medico-legal point of view (R13, Evidence D). The patient is also asked to make his 'allergies' known prior to all prescriptions and surgical operations.

Preventive measures by premedication (e.g., slow injection and pretreatment with glucocorticosteroids and H1-antihistamines) are useful mainly for nonallergic DHRs (for example to vancomycin, some NMBA, iodinated RCM, and chemotherapy drugs) (R14, Evidence C). Corticosteroids and H1-antihistamines may not reliably prevent IgE-dependent anaphylaxis (103).

Desensitization

Drug desensitization is defined as the induction of a temporary state of clinical unresponsiveness/tolerance to a compound responsible for a DHR (6, 19). Several other terms have been utilized in the past. To encompass classic IgE- and non-IgE-mediated drug desensitization, the Practice Parameters (6) introduced the term 'induction of drug tolerance'. Except for aspirin, the BSACI guidelines only propose desensitization related to an IgE-mediated mechanism (8).

The possibility of desensitization should always be considered when the offending drug is essential and when either no alternatives exist or they are unsatisfactory, as in the following cases (6, 19): sulfonamides in HIV-infected patients (107), quinolone allergies in some patients with cystic fibrosis, serious infections with allergy to β-lactams, antituberculosis drugs, allergy to tetanus vaccine, hemochromatosis with allergy to desferoxamine, taxanes, and platinum salt-based cancer chemotherapeutic agents (108), monoclonal antibodies utilized in several types of hematological and nonhematological neoplasms, aspirin and NSAID hypersensitivity in patients for whom the necessity for these drugs to treat either a cardiac (109) or rheumatic disease is clear.

There are no generally accepted protocols for drug desensitization in immediate DHRs, and guidelines (19) recommend referral to successfully applied existing protocols (R15, Evidence C). For nonimmediate DHRs, the literature is less extensive and more controversial. For EAACI-DAIG/ENDA experts, desensitization in delayed DHRs has to be restricted to uncomplicated exanthemas or fixed drug eruption, due to the unpredictability and limited therapeutic options in severe DHRs (110). Desensitization to aspirin, as a therapeutic intervention for aspirin-exacerbated respiratory disease or nasal polyps, is briefly mentioned by EAACI-DAIG/ENDA guidelines (19), whereas it is recommended in properly selected asthmatic patients by the US Practice Parameter (6), based on certain published data (111) (R16, Evidence D).

General preventive measures

General preventive measures include a declaration to the Committee on Safety of Medicine Reports. The reporting of DHRs leads to public health inquiries and decisions. Some successful examples of proper reports are the rules concerning the use of penicillins during animal feeding, the withdrawal from the market of glafenine, the reformulation of propofol to eliminate the need for Cremophor EL (castor oil) and its replacement with other lipids, and the warnings concerning abacavir, carbamazepine, and nevirapine.

Unmet needs

Unmet clinical needs

Drug hypersensitivity reactions have a significant impact on clinical practice, drug development, and healthcare expenditures. However, epidemiological studies or research to increase understanding and to develop diagnostic and predictive tests has been limited. Epidemiologic risk factors for DHRs are not well characterized and may be influenced by regional/national differences in drug prescriptions and by genetic markers. All drugs can induce DHRs, but the incidence and risk factors for individual drugs remain a major unmet need. As an example, the co-medication of diclofenac with antiulcer medications may present a novel potentiating factor (112), as could the use of over-the-counter pholcodine regarding NMBA-induced anaphylaxis (113). The development of a network to increase the population size from which data on DHRs can be captured would be a major advance. This approach would aim to overcome the major limitation of spontaneous reporting, that is, under-reporting or non-proven case reporting, by engaging with interested clinicians and involving them in the network.

Physicians do not always have the confidence to clarify a suspected reaction. When they do so, and refer the patients to specialized centers, each one of them experiences a limited and partly biased spectrum of the disease (114). Although standardized diagnostic procedures have been published, validation of these clinical tests for all drugs does not exist and multicenter multinational studies are needed for this purpose. Current controversies and disagreements between the guidelines need to be addressed by further research (e.g., skin testing for iodinated RCM, NPV for penicillin skin testing, utility of skin testing for a variety of rare DHRs (steroids, preservatives, etc), and desensitization for delayed DHRs). Standardized diagnostic procedures should be tailored to specific drugs (e.g., β-lactam antibiotics, non-β-lactam antibiotics, NSAIDs, local anesthetics, radiocontrast media, chemotherapeutic agents, vaccines, biological agents), specific manifestations, and specific age groups (children *vs* adults). New diagnostic tools should be developed, in particular for the diagnosis of severe cutaneous DHRs, or DHRs those affecting internal organs including the liver, lungs, kidneys, and bone marrow. The development of tools for skin testing and biological diagnosis is indeed crucial for those cases where DPT is not possible. Standardized and widely accepted drug allergy procedures are crucial for both individual patient genotyping–phenotyping and epidemiological studies. There should be education in medical schools and residencies as well as postgraduate training programs that include aspects of DHR and its treatment, as well as funding for the postgraduate education of specialists.

The impact of DHRs on the quality of life of patients and their cost on the healthcare system, probably substantial, is

unknown. For this, one must take into account not only the direct costs (treatment of these reactions, hospitalizations, and prolongation of hospitalization), but also the indirect costs (sick leave, invalidity, excessive cost of the choice of alternatives which are not always medically satisfactory and which may lead to specific adverse effects including the induction of microbial resistance and reduced efficacy).

Additionally, most therapeutic recommendations, including new approaches such as drug desensitization, are mostly based on case reports or small case series. As we do not know the natural course of DHRs, it is not clear whether lifelong avoidance is really necessary. Specific research dedicated to the treatment for anaphylaxis should also be supported. DHR research has not been supported for a long time neither by the pharmaceutical industry nor by national programs. There is therefore a clear need for training, standardized criteria, and large, multicenter studies. The establishment of multinational, adequately resourced large DHR databases/registries would enable all observations to be collected, which would in turn facilitate epidemiologic, risk factor, pharmacovigilance, and research analyses.

Unmet basic research needs

The availability of tissue and serum samples from DHR patients is a prerequisite for basic research in the mechanism of DHRs, which may be allergic or nonallergic, with immunological or pharmacological recognition and with the allergenic and genetic determinants mostly unknown.

Evidence over the past ten years suggests that not all drugs need to bind covalently to the MCH in order to induce an immune response. Without undergoing the classical antigen processing and presentation pathway, some drugs may bind directly in a noncovalent fashion to immune receptors, triggering a drug-specific immune reaction (the p-i concept) and promoting an exchange of embedded peptides (38). The functional consequence of this peptide exchange should be further analyzed. This may explain the increased susceptibility of some patients and the frequency of non-IgE-mediated reactions that occur within hours of first exposure. Whether or not this mechanism is also involved in IgE-dependent reactions is not yet known. The prediction of such reactions may also be possible, but has not yet been fully evaluated. The importance here lies in future drug development, the prediction of which molecules may participate in such reactions, and the development of congeners which retain pharmacological activity, but do not cause immune reactions. For most drugs, the allergenic determinants are unknown. The lack of complete understanding of DHR mechanisms probably explains the low sensitivity of many skin tests and *in vitro* assays. There are many examples where existing tests are negative, and this is likely to be related to the use of an inappropriate antigen. Pinpointing the allergenic determinants is of crucial importance; this will allow a better prediction of cross-reactivities and will provide clinicians with tools for skin testing, biomarkers, and biological diagnosis. A better understanding of virus–drug interactions is also crucial. The availability and use of appropriate viral tests are a prerequisite for a proper evaluation of the role of viral infections in DHRs.

Genetic differences can affect individual responses to drugs by influencing the way in which the drug is processed or acts in the body. They may explain why some drugs induce an immune reaction in only a minority of individuals. Genetic variation in the activity of enzymes and carrier substances can be responsible for changes in the absorption, transport, metabolism, and excretion of drugs. Some genetic variants in (i) drug-metabolizing enzymes (pharmacogenetics) interfering with oxidation, conjugation, and hydrolysis (cytochrome P450, glucuronyl transferase, and glutathione S transferase), acetylation; (ii) drug receptors and effector proteins; and (iii) genes controlling the immune response, especially in the MCH molecules (immunogenetics), have been associated with some DHRs (Table 3). This is an emerging field, which holds a great deal of promise for the development of individual predictive tests. However, this will only be possible if we can pool resources to identify and characterize a large cohort of patients with standardized phenotypic definitions to design studies with adequate statistical power (61). This will only be possible through collaboration.

To generate preclinical testing methods to assess the risk of potential DHRs in new drugs, research should encompass the characterization of drug-specific (chemical structure, metabolites, exposure), intrinsic (genetics), and extrinsic (viral infections, other danger signals) risk factors, complemented by preclinical prediction models (2, 115).

Conclusions

The diagnosis of DHRs is often challenging and requires the same careful approach, no matter which specific drug is involved. It remains largely clinical with the help of certain allergy tests that are available for some of the drug classes. Provocation tests are the gold standard for determining current tolerance, but require expertise, carry a certain amount of risk, and are limited to highly specialized centers when used to establish or rule out diagnosis. They cannot be applied for severe cutaneous reactions. New and validated biological tests for diagnosis, available to all clinicians, are necessary in order to improve care for these patients. Recently, HLA typing has provided an important tool for detecting susceptible patient populations. In view of the diagnostic uncertainty of most adverse drug reaction studies (1), the epidemiology of DHRs was not covered in this ICON document. However, understanding the epidemiology of adverse drug reactions in general and DHRs in particular remains an important future research priority. Finally, collaborative basic research into the pathophysiology of DHRs should be intensified in order to better understand this complex set of diseases associated with or induced by drug exposures and mediated (or not) by the immune system.

Conflicts of interest

The authors declare no conflicts of interest for this work.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Drug hypersensitivity questionnaire (adapted from (11) with permission).

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Fixed drug eruption

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Fixed drug eruption

INTRODUCTION — Fixed drug eruption (FDE) is a distinctive type of cutaneous drug reaction that characteristically recurs in the same locations upon reexposure to the offending drug. Acute FDE usually presents with a single or a small number of dusky red or violaceous plaques that resolve leaving postinflammatory hyperpigmentation (picture 1A-C). Rare severe atypical variants of FDE, including multiple, nonpigmenting, and generalized bullous variants, share clinical features with Stevens-Johnson syndrome/toxic epidermal necrolysis.

FDE will be discussed in this topic. Other types of drug eruptions are discussed separately. (See "Drug eruptions" and "Exanthematous (morbilliform) drug eruption" and "Lichenoid drug eruption (drug-induced lichen planus)" and "Stevens-Johnson syndrome and toxic epidermal necrolysis: Pathogenesis, clinical manifestations, and diagnosis".)

EPIDEMIOLOGY — Cutaneous skin reactions occur in approximately 2 to 3 percent of patients taking drugs. Fixed drug eruptions (FDE) are less common than exanthematous (morbilliform) eruptions, which are estimated to account for up to 95 percent of cutaneous drug reactions [1-3]. FDEs occur in both sexes and in all age groups; in children, FDEs account for 14 to 22 percent of cutaneous drug reactions [4,5].

ETIOLOGY AND PATHOGENESIS

Eliciting drugs — Many drugs may induce fixed drug eruptions (FDE). The frequency with which individual drugs cause FDE varies over time and from country to country, depending upon drug availability and rates of consumption. Drugs most frequently associated with FDE include [6-8]:

- Antibacterial agents (trimethoprim-sulfamethoxazole, tetracyclines, penicillins, quinolones, dapsone)
- NSAIDs (acetylsalicylic acid, ibuprofen, naproxen, mefenamic acid)
- Acetaminophen (paracetamol)
- Barbiturates
- Antimalarials

Immunologic mechanisms — Intraepidermal $CD8^+$ T cells are thought to have a key role in mediating the localized epidermal lesion that characterizes FDE [9]. $CD8^+$ T cells with an effector–memory phenotype are abundantly detected along the dermoepidermal junction in established FDE lesions and persist in resting FDE lesions long after the clinical resolution (picture 2A-B) [9-13].

Sequential analysis of FDE lesions before and after rechallenge with the causative drug demonstrated that intraepidermal $CD8^+$ T cells are directly involved in epidermal damage (picture 3) [14]. $CD8^+$ T cells remain quiescent but in a primed state in healed FDE lesions unless the causative drug is readministered. Upon rechallenge, $CD8^+$ T cells are activated to release interferon gamma and cytotoxic granules such as granzyme B and perforin [12-14]. Mast cells also contribute to the activation of intraepidermal T cells via the induction of cell adhesion molecules on the surrounding keratinocytes, through the action of tumor necrosis factor alpha [13].

The activation of intraepidermal T cells is sufficient for triggering the reaction but insufficient to cause the extensive tissue damage observed in fully evolved lesions. Cytokines and/or adhesion molecule-mediated recruitment of $CD4^+$ T cells, $CD8^+$ T cells, and neutrophils may contribute to tissue damage in fully developed FDE lesions.

In the late stage of the immune response, $CD4^+CD25^+Foxp3^+$ regulatory T (Treg) cells are recruited into the lesion and participate in the homeostatic control of the immune reaction. The majority of the expanded or activated cell populations responsible for epidermal damage are eventually removed from tissue by apoptosis. However, a proportion of intraepidermal $CD8^+$ T cells is prevented from undergoing apoptosis by IL-15 secreted by basal keratinocytes and persists at the injury site as a memory T cell population [14,15].

HISTOPATHOLOGY — Histologically, FDE is the prototype of a lichenoid tissue reaction with pigmentary incontinence (accumulation of melanin in the upper dermis and dermal macrophages) [16]. In florid lesions, major features include hydropic degeneration of basal keratinocytes, dyskeratotic cells scattered in the epidermis, lymphocytic infiltration of the dermis, and dermal melanophages. The hair follicles and acrosyringia (the intraepidermal

portions of the sweat gland duct) also may be involved. In some lesions, the exocytosis of lymphocytes is marked, mimicking Pautrier microabscesses of mycosis fungoides.

Healed hyperpigmented lesions show pigmentary incontinence and a mild perivascular inflammatory infiltrate.

The pathologic changes occurring in a resting lesion after reexposure to the offending drug have been documented by sequential biopsies [14]:

- Resting FDE lesions are characterized by a small number of resident $CD8^+$ lymphocytes aligned along the epidermal side of the dermoepidermal junction (picture 2A-B). The overlying epidermis appears normal (picture 3).

- Two to three hours after rechallenge, the lymphocytes originally adhering to the basal layer move upward to the lower one-half of the epidermis while preserving the epidermal structures.

- Twenty-four to 48 hours after rechallenge, the typical changes of interface dermatitis can be seen, including vacuolar degeneration of keratinocytes, dermal lymphocytic infiltrate extending upward into the epidermis, and dermal pigmentary incontinence. The extent of epidermal damage is highly variable, ranging from intercellular edema and dyskeratotic cells scattered in the epidermis to confluent epidermal necrosis resembling TEN.

Several atypical histologic reaction patterns have been described in FDE, including a neutrophilic reaction, leukocytoclastic vasculitis, and nonpigmenting FDE (NPFDE) [17-20]. In NPFDE, the epidermal changes are mild or absent and a superficial perivascular infiltrate of lymphocytes and eosinophils without melanophages is seen in the upper reticular dermis. In generalized bullous FDE, the histologic features of the blister area closely resemble those seen in SJS/TEN (full-thickness necrosis of the epidermis without pigmentary incontinence) [21].

CLINICAL MANIFESTATIONS — Fixed drug eruption (FDE) typically presents with well demarcated, round to oval, dusky red to brown/black macules that may evolve into edematous plaques with or without vesiculation or blistering (picture 1A-B, 1D). Lesions are usually solitary, buy may occur in small groups.

Systemic symptoms, such as fever and malaise, are usually absent. Pruritus and a burning or stinging sensation are common. However, the estimated frequency of these findings is not known because they are not consistently reported in case series.

FDE may occur anywhere on the body. Sites of predilection include the lips, genitalia, perianal area, hands, and feet [22]. On mucosal areas, erosions and ulcers may develop (picture 1E). FDE occasionally develops at the site of an antecedent trauma (eg, insect bite, burn, venipuncture) [23,24].

Acute lesions generally appear 30 minutes to 8 hours after drug administration, but can occur up to two weeks after drug exposure [7,25]. After discontinuation of the offending drug, lesions resolve spontaneously in 7 to 10 days, leaving a persistent gray/brown or slate gray postinflammatory hyperpigmentation (picture 1C).

Upon reexposure to the offending drug, lesions typically recur in the same site, but new lesions may develop elsewhere (picture 4). After one or more localized eruptions, FDE rarely

may evolve into a bullous generalized form mimicking Stevens-Johnson syndrome/toxic epidermal necrolysis (picture 5). (See 'Generalized FDE' below and 'Generalized bullous FDE' below.)

FDE can be induced by drugs with a chemical structure similar to the causative drug (cross-reactivity). There are isolated reports of FDE lesions reactivated by chemically unrelated drugs, a phenomenon known as polysensitivity [26,27].

CLINICAL VARIANTS — Fixed drug eruption (FDE) rarely may present with atypical features that mimic other skin diseases such as erythema multiforme, Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), cellulitis, paronychia, neutrophilic dermatosis, or large-plaque parapsoriasis.

Erythema multiforme-like FDE — FDE may present with targetoid lesions that mimic erythema multiforme (picture 6). In contrast to erythema multiforme, these lesions have only two concentric zones of color with a darker, dusky hue in the center. (See "Pathogenesis, clinical features, and diagnosis of erythema multiforme", section on 'Clinical manifestations'.)

Generalized FDE — The typical lesions are multiple and disseminated and involve the trunk and extremities, sparing the mucosal and the semi-mucosal areas (picture 7). Generalized FDE may be difficult to distinguish clinically and histologically from erythema dyschromicum perstans (picture 8) [28].

Generalized bullous FDE — Generalized bullous fixed drug eruption (GBFDE) is an extremely rare form of FDE characterized by widespread red or brown macules or plaques with overlying large flaccid bullae (picture 5) [29]. Systemic symptoms, such as fever, malaise, or arthralgias may be present.

Patients with GBFDE can be misdiagnosed as having SJS/TEN, but in GBFDE mucosal involvement is usually absent or mild and the clinical course is favorable with rapid resolution in 7 to 14 days after drug discontinuation [30-32].

However, the prognosis of GBFDE may be unfavorable in older patients, particularly in those with comorbidities.

In a case-control study including patients with GBFDE (age range 68 to 84 years) and matched controls with SJS/TEN, the mortality rate among patients with GBFDE was 22 percent, similar to that observed among patients with SJS/TEN with the same amount of skin detachment [33]. (See "Stevens-Johnson syndrome and toxic epidermal necrolysis: Pathogenesis, clinical manifestations, and diagnosis", section on 'Clinical presentation'.)

Nonpigmenting FDE — Nonpigmenting fixed drug eruptions (NPFDE) have been described in a small number of patients, most often in association with the administration of pseudoephedrine. NPFDE presents with large solitary or multiple, well-circumscribed erythematous plaques that resolve without postinflammatory hyperpigmentation [17,34].

A severe form of NPFDE, characterized by disseminated, large, symmetrical plaques and systemic symptoms may be misdiagnosed as SJS/TEN.

Other variants — Other rare forms of FDE have been described in isolated reports and include [35-37]:

- FDE presenting with acute paronychia
- FDE presenting with a linear distribution reminiscent of herpes zoster
- FDE mimicking large-plaque parapsoriasis

DIAGNOSIS

Clinical — The diagnosis of fixed drug eruption (FDE) in its typical presentation is usually straightforward, based upon lesion morphology and history:

- Single or a small number of round or oval, demarcated, erythematous or hyperpigmented macules or plaques located most often on the lips, genitalia, and extremities (picture 1A-B, 1E).

- History of drug intake in the hours or days preceding the eruption. The medication history should be taken in great detail and include all types of medications and routes of administration, since patients tend to overlook medications that they have been taking sporadically over years. (See "An approach to the patient with drug allergy", section on 'Identification of the suspect drug'.)

- History of recurrence in the same sites following the administration of the same drug or a chemically related drug.

Biopsy — A skin biopsy for histopathologic examination may be warranted in the following circumstances:

- Unusual clinical presentation (eg, generalized or bullous FDE) that raises the suspicion of severe drug reaction
- Presence of systemic symptoms (eg, fever, malaise)
- When the diagnosis is uncertain (eg, negative medication history)

Histologic findings that support the diagnosis of FDE include hydropic degeneration of the basal layer, pigmentary incontinence, single necrotic keratinocytes (dyskeratotic cells) in the upper layers of the epidermis, and a dermal inflammatory infiltrate predominantly composed of lymphocytes. In generalized bullous FDE, the examination of a biopsy taken from the blister area reveals full-thickness necrosis of the epidermis without pigmentary incontinence. (See 'Histopathology' above.).

Provocation tests — Systemic (oral challenge) and topical (patch testing) provocation tests can be performed to identify the culprit drug when history is unclear or multiple medications are suspected [6,15].

Systemic provocation — Oral challenge with the suspected drug induces the reactivation of a resting FDE lesion. In most cases, oral challenge is preferred to patch testing because it reproduces the conditions of exposure.

Oral challenge is contraindicated in patients with a history of generalized FDE. In patients without generalized FDE, oral challenge is considered relatively safe because the cutaneous response is localized and the risk of a severe reaction is low. In a series of 450 patients with FDE, oral challenge with the suspected drug produced pruritus in 10 percent of patients, fever in 0.9 percent, and generalized urticaria in 0.7 percent, but no more severe adverse effects [6].

However, neither the appropriate dose of the suspected drug sufficient to induce a mild reaction nor the timing of the test after the resolution of the initial eruption has been standardized. Our approach is to perform the test two to four weeks after the resolution of the eruption, starting with one-tenth of a single therapeutic dose and gradually increasing the amount every 12 to 24 hours up to one single therapeutic dose. Others may use a different approach. In a prospective series of 93 patients with FDE, oral challenge was started with one-half of the therapeutic dose; if no reaction was elicited, a full dose was given [38].

A flare-up reaction occurring within 30 minutes to 8 hours of the oral challenge within a resting FDE lesion is considered a positive test response (picture 4) [15].

Patch testing — Patch testing also can be used to confirm the diagnosis if oral testing cannot be performed (eg, patients with a history of generalized FDE) or if the patient or parent refuses an oral challenge. Patch testing can be performed by applying the suspected drug to an old FDE lesion to elicit a local reaction. Patch testing is generally considered to be safe because the reaction is localized.

There is no standardized method for patch testing in FDE. Various drug concentrations and application modalities (eg, single open, repeated open, or occlusive) have been used in several series of patients [7,8,39,40].

Our approach is to use the commercially available drug mixed in petrolatum or diluted in water at the concentration of approximately 10 to 20 percent. The drug is applied to the target area in open or occlusive modality. The development of erythema with or without induration that starts within 24 hours and lasts for at least 6 hours is considered a positive reaction (picture 9) [39].

False negative results may occur when testing drugs with limited ability to penetrate into the skin or when FDE is caused by a drug metabolite [15]. False positive reactions may be observed with drug concentrations higher than 20 percent due to patch test sensitization. (See "Patch testing", section on 'Active sensitization'.)

DIFFERENTIAL DIAGNOSIS — The differential diagnosis of fixed drug eruption (FDE) includes:

Erythema multiforme – Erythema multiforme (EM) is rarely induced by drugs. The number, distribution, and morphology of lesions help to differentiate EM from FDE. Target lesions consisting of three components (a dusky central area or blister, a dark red inflammatory zone surrounded by a pale ring of edema, and an erythematous halo) are the hallmark of EM (picture 10). They are generally numerous and symmetrically distributed on the extremities. Mucosal lesions are present in many cases (EM majus) (picture 11). (See "Pathogenesis, clinical features, and diagnosis of erythema multiforme", section on 'Clinical manifestations'.)

Stevens-Johnson Syndrome/Toxic epidermal necrolysis – Generalized bullous fixed drug eruption (GBFDE) may sometimes be difficult to differentiate from Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) (picture 12). However, in SJS/TEN, lesions have a less defined border than FDE lesions with a tendency to coalesce; mucous membranes (eg, oral, conjunctival) are involved in over 90 percent of cases (picture 13); and patients have systemic symptoms and rapid disease progression.

The histologic features in the early stage of SJS/TEN are similar to those of GBFDE [32]; however, as the disease progresses, full thickness epidermal necrosis with skin detachment above the basement membrane becomes evident. In most patients, GBFDE resolves rapidly in 7 to 14 days after drug discontinuation [30,31]. The course of SJS/TEN is generally longer than in GBFDE and complications and sequelae (eg, sepsis, organ failure, late ophthalmic and pulmonary complications) are frequent. (See "Stevens-Johnson syndrome and toxic epidermal necrolysis: Management, prognosis, and long-term sequelae", section on 'Long-term sequelae' and "Stevens-Johnson syndrome and toxic epidermal necrolysis: Pathogenesis, clinical manifestations, and diagnosis".)

Bullous pemphigoid – Bullous pemphigoid (BP) typically occurs in patients older than 60 years and is frequently preceded by a prodromal phase characterized by pruritic inflammatory plaques resembling urticaria. The typical skin lesions of BP are large, tense blisters that rupture and heal spontaneously without scarring (picture 14). Histology reveals a subepidermal blister with a dermal infiltrate of eosinophils, neutrophils, and lymphocytes (picture 15). Direct immunofluorescence of perilesional skin shows linear IgG and/or linear C3 staining along the basement membrane zone (picture 16), which is absent in FDE. The diagnosis of BP can be confirmed by enzyme-linked immunosorbent assay demonstrating circulating autoantibodies against the bullous pemphigoid antigens BP180 NC16A domain and BP230. (See "Clinical features and diagnosis of bullous pemphigoid and mucous membrane pemphigoid", section on 'Clinical features' and "Clinical features and diagnosis of bullous pemphigoid and mucous membrane pemphigoid", section on 'Diagnosis'.)

Large-plaque parapsoriasis – Large-plaque parapsoriasis may resemble the pigmented patches of FDE (picture 17A-B). A skin biopsy is necessary to clarify the diagnosis. Histology reveals epidermal hyperplasia (or atrophy in poikilodermatous areas) and a dermal lymphocytic infiltrate that can become band-like at the dermal epidermal junction and show epidermotropism (exocytosis of small lymphocytes into the epidermis).

MANAGEMENT

Drug withdrawal and avoidance — Discontinuation of the offending drug is the most important aspect of management of FDE. After drug discontinuation, lesions resolve without treatment in a few days leaving postinflammatory hyperpigmentation.

Patients should be advised to avoid the offending drug and chemically related drugs and be provided with a written list of the generic and brand names of the culprit drug and possibly of cross-reactive drugs.

Symptomatic treatment — The treatment of FDE is largely symptomatic and aimed at the relief of pruritus. The efficacy of symptomatic therapies for the treatment of FDE has not been evaluated in randomized trials. However, their use is based on clinical experience and indirect evidence of benefit in patients other pruritic skin conditions. (See "Pruritus: Overview of management".)

- For patients with single or a small number of lesions, we suggest medium to high potency topical corticosteroids (groups one to three (table 1)) and systemic antihistamines. Topical corticosteroids are applied two times per day for 7 to 10 days. Oral H1 antihistamines are generally used, including:

    - Diphenhydramine – 25 to 50 mg orally every four to six hours for adults and children ≥12 years; 12.5 to 25 mg orally every four to six hours for children 6

to 11 years; and 6.25 mg orally every four to six hours for children 2 to 5 years. Diphenhydramine is continued until pruritus subsides.

- Hydroxyzine – 25 mg orally three to four times per day for adults and children ≥6 years; 2 mg/kg per day orally divided every six to eight hours for children <6 years. Hydroxyzine is continued until pruritus subsides.

- For patients with generalized FDE or generalized bullous FDE, particularly if systemic symptoms are present, a short course of moderate dose systemic corticosteroids (eg, prednisone 0.5 to 1 mg/kg per day for three to five days) may be beneficial.

SUMMARY AND RECOMMENDATIONS

- Fixed drug eruption (FDE) is a cutaneous drug reaction that characteristically recurs in the same locations upon reexposure to the offending drug. Antibacterial sulfonamides, antibiotics, nonsteroidal antiinflammatory drugs, analgesics, and hypnotics are the most frequent causes of FDE. (See 'Introduction' above and 'Eliciting drugs' above.)

- FDE typically presents with solitary round to oval, dusky red to brown/black macules that may evolve into edematous plaques or bullae (picture 1A-B, 1D). Sites of predilection include the lips, genitalia, perianal area, and extremities. Acute lesions usually develop 30 minutes to 8 hours after drug administration and resolve spontaneously in 7 to 10 days, leaving a persistent gray/brown or slate gray postinflammatory hyperpigmentation (picture 1C). (See 'Clinical manifestations' above.)

- In rare cases, FDE may present with atypical features, including generalized bullous FDE and nonpigmenting FDE that mimic more severe drug eruptions such as Stevens-Johnson syndrome/toxic epidermal necrolysis (picture 5). (See 'Clinical variants' above.)

- The diagnosis of fixed drug eruption (FDE) in its typical presentation is usually straightforward, based upon lesion morphology and history. Histologic examination of a skin biopsy is helpful in establishing the diagnosis in cases with unusual clinical features. (See 'Clinical' above and 'Biopsy' above.)

- Systemic or topical provocation tests may be helpful in identifying the culprit drug when history is unclear or multiple medications are suspected. (See 'Provocation tests' above.)

- Discontinuation and avoidance of the offending drug is the most important aspect of management of FDE. Symptomatic treatment of the acute eruption may include medium to high potency topical corticosteroids (groups one to three (table 1)) and systemic antihistamines. (See 'Drug withdrawal and avoidance' above and 'Symptomatic treatment' above.)

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