Patch Testing in Drug Eruptions: Practical Aspects and Literature Review of Eruptions and Culprit Drugs

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Abstract: **There is overwhelming evidence that many delayed cutaneous adverse drug reactions (beginning >6 hours after drug intake) are mediated by delayed-type (type IV) hypersensitivity, including maculopapular eruptions, erythroderma, symmetrical drug-related intertriginous and flexural exanthema/baboon syndrome, eczematous eruptions, fixed drug eruptions, acute generalized exanthematous pustulosis, and drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome. Therefore, after resolution of the reaction, patch tests should be performed as first diagnostic method to identify the culprit drug(s). This article provides tools to perform drug patch tests properly and safely, discussing clinical history, indications, procedure, drug patch test materials, sensitivity, the meaning of negative patch tests, and safety of the procedure. In addition, a literature review of eruptions and culprit drugs is provided in tabular format.**

BULLET POINTS

- Patch testing is a valuable diagnostic tool for identifying culprit drugs in delayed cutaneous adverse drug reactions (drug eruptions).
- They should be performed 6 weeks to 6 months after complete resolution of the drug hypersensitivity reaction.
- Sensitivity is (relatively) high in eczematous eruptions, erythroderma, maculopapular eruptions, acute generalized exanthematous pustulosis, drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome, and the abacavir hypersensitivity syndrome.
- A negative patch test does not exclude a causal role for the drug tested in the eruption; a next diagnostic step is necessary, usually intradermal tests with delayed reading.

Drug hypersensitivity reactions (DHRs) are adverse effects of drugs that clinically resemble allergic reactions. They are called drug allergies when a definite immunological mechanism (either drug-specific antibody or T cell mediated) has been demonstrated.[1] Drug hypersensitivity reactions affect more than 7% of the population[2] and 5% of hospitalized patients, and are associated with significant morbidity and mortality.[3] Based on the time between drug exposure and onset of symptoms/signs, reactions may be divided into immediate and nonimmediate (delayed) hypersensitivity reactions. Immediate reactions tend to occur within minutes to 1 hour after drug administration, but may develop after 1 to 6 hours. Symptoms are mostly urticaria (with or without angioedema), sometimes progressing to more severe symptoms, such as bronchospasm, hypotension, and anaphylactic shock.[1] Nonimmediate hypersensitivity reactions occur mostly later than 6 hours, often 24 hours, after drug intake. Maculopapular eruptions are the most frequent manifestation of this type.[2–5] Antibiotics are often implicated in both immediate and delayed adverse drug reactions, especially aminopenicillins, such as amoxicillin and ampicillin.

Physicians who care for patients with delayed cutaneous adverse drug reactions (CADRs) are often faced with diagnostic difficulties. Cutaneous adverse drug reactions may present in many forms, and although it is well known which drugs and drug classes are frequently implicated in defined clinical manifestations (eg, penicillins in maculopapular eruptions, aromatic antiepileptics in drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome [DRESS/DIHS]), the various CADRs are not characteristic for specific drugs. Individual drugs can cause a variety of drug eruptions, and specific drug eruptions can be caused by a great many pharmaceuticals. Also, patients often use multiple drugs, which makes it difficult to identify the responsible agent based on the clinical picture and patient history alone.

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Once the DHR has been resolved, a search for the culprit drug should be undertaken. Making a diagnosis on the clinical history alone (even when performed thoroughly) is often unreliable and may lead to unjustified use or avoidance of indicated drugs.[1,3] Overwhelming evidence suggests that the nonimmediate drug eruptions are caused by delayed-type, T cell–mediated hypersensitivity to the drugs.[6] Therefore, patch tests, prick tests, and intradermal tests (the latter 2 with delayed reading) may identify the offender, they can differentiate sensitization to the drug itself from a reaction to excipients and can also aid in finding a replacement drug.[7] The usefulness of these skin tests in delayed-type drug eruptions has been ascertained in many investigations.[8–16] Other clinical tools allowing a definitive diagnosis include *in vitro* tests (eg, lymphocyte transformation test) and drug provocation tests. Diagnostic testing in nonimmediate DHRs has been extensively reviewed in the last 14 years.[1,4,5,7,17–25]

In the opinion of the author, patch testing should always be the first diagnostic test in patients with drug eruptions. They are easy to perform (ie, by experts), standardized, cheap, and not burdensome to the patient. Most importantly, a positive patch test reaction abolishes the need for other tests. Also, it is the only *in vivo* diagnostic test that can generally be considered safe, even in the more severe CADRs. It must be stressed that optimal results of patch testing in drug eruption can only be obtained with flawless technique. Therefore, where many patients with the more severe DHRs have systemic symptoms and are first treated by internists or other specialists, the dermatologist should always be consulted at the start of the diagnostic route searching for the culprit drug(s).

This article provides information that enables dermatologists to perform patch tests in drug eruptions adequately. In addition, a full literature review of drug reactions caused by systemic drugs, in which patch tests were positive, is provided in tabular format. This text is adapted from chapters 2 and 4 of the author's book *Monographs in Contact Allergy, Volume 4: Systemic Drugs.*[6] For diagnostic tests other than patch tests (prick, intradermal, drug provocation, *in vitro* tests), the reader is referred to the review articles mentioned previously and to the studies of Barbaud et al[26] (technique of intradermal testing), Aberer et al[27] (drug provocation tests), and Brockow et al[3] (nonirritant concentrations for prick and intradermal tests). However, dermatologists should never start performing these procedures before having acquired a thorough knowledge of their indications, techniques, and risks and preferably have followed expert training.

PATCH TESTING IN DRUG ERUPTIONS

Clinical History

The patient's clinical history must be carefully obtained and should include the symptomatology, previous exposure, delay between the last dose and the onset of symptoms, effect of stopping treatment, medications taken (both at the time of the reaction and other drugs taken since then), and the medical background of the patient (any suggestion of a previous allergy, whether associated with medication or not, or of a medical condition).[1] Sensitization to drugs takes a minimal period of 4 to 5 days. The latency period, the time from first treatment to presentation of the drug eruption, averages 4 to 12 days in maculopapular eruptions, 8 days in abacavir hypersensitivity syndrome (which is often considered to be a form of DRESS/DIHS), 2 to 8 weeks in DRESS/DIHS, 4 to 28 days in Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), and 4 days to weeks in other eruptions. Once sensitized, the reaction/eruption may start within a few hours after renewed drug administration.[4] Data should ideally be recorded in a uniform format, which have been developed and are available in many languages.[28]

Indications

Delayed DHRs in which patch tests may be diagnostically helpful are shown in Table 1. They are often divided into nonsevere and severe CADRs. To the nonsevere category belong *inter alia* eczematous eruption, maculopapular eruption, fixed drug eruption, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE),

TABLE 1. Delayed CADRs (Adapted from the Study of De Groot[6])

CADR	Sensitivity of Patch Testing
Nonsevere CADRs	
Eczematous eruption	33%–53%
Erythema multiforme-like eruption	8%–21%
Erythroderma, widespread erythematous eruption, exfoliative dermatitis	53%–71% (erythroderma)
Fixed drug eruption	0%–79%
Lichenoid drug eruption	18%
Localized hypersensitivity reactions to subcutaneous injections (eg, heparins, local anesthetics)	High
Maculopapular eruption	14%–59%
Photoallergic dermatitis	50%–100%
SDRIFE/baboon syndrome	51%
Systemic allergic dermatitis (systemic contact dermatitis)	100% (presensitization required)
Urticaria/angioedema (delayed)	12%
Other less defined drug eruptions	
Severe CADRs (SCARs)	
Abacavir hypersensitivity syndrome (often considered to be a form of DRESS/DIHS)	>80%
AGEP	0%–65%
DRESS/DIHS	32%–83%
Generalized bullous fixed drug eruption	No adequate data available
SJS/TEN	0%–24%

AGEP, acute generalized exanthematous pustulosis; CADR, cutaneous adverse drug reaction; DRESS/DIHS, drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome; SCARs, severe CADRs; SDRIFE, symmetrical drug-related intertriginous and flexural exanthema; SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.

TABLE 2. Systemic Drugs Commercially Available for Patch Testing (Adapted from the Study of De Groot[6])*

Patch Test Allergen (Hapten)	Chemotech	SPCanada	SPEurope
Acetaminophen (paracetamol)	10.0%	10%	
Acetylsalicylic acid	10.0%		
Acyclovir	10.0%		
Articaine hydrochloride		1%	
Aminophenazone		10%	
Amoxicillin trihydrate	10.0%		
Ampicillin		5%	5%
Benzydamine hydrochloride	2.0%	1%; 2%	
Betamethasone dipropionate	1.0%	0.5%; 0.1% alc.	
Captopril	5.0%		
Carbamazepine	1.0%		
Cefalexin	10.0%		
Cefixime trihydrate	10.0%		
Cefotaxim sodium salt	10.0%		
Cefpodoxime proxetil	10.0%		
Cefradine	10.0%		
Cefuroxime sodium	10.0%		
Chloramphenicol	5.0%	5%; 2% alc.	5%
Chlorpheniramine maleate		5%	
Chlorpromazine hydrochloride	0.1%	1%	1%
Chlortetracycline hydrochloride		1%	
Ciprofloxacin hydrochloride	10.0%		
Clarithromycin	10.0%		
Clavulanate potassium	10.0%		
Clindamycin phosphate	10.0%		
Clioquinol	5.0%	5%	5%
Cotrimoxazole	10.0%		
Dexamethasone		0.5%	
Dexamethasone-21-phosphate		1%	
Dexamethasone-21-phosphate disodium salt	1.0%		1%
Dexketoprofen	1.0%	1%	
Diclofenac		2.5%; 5%	2.5%
Diclofenac sodium salt	1.0%; 5.0%		
Dicloxacillin sodium salt hydrate	10.0%		
Diltiazem hydrochloride	10.0%		
Diphenhydramine hydrochloride	1.0%		
Doxycycline monohydrate	10.0%		
Erythromycin base	10.0%	1%; 2%	2%
Fenofibrate	10.0%	10%	
Fusidic acid sodium salt	2.0%	2%	
Gentamicin sulfate	20.0%	20%	20%
Hydrochlorothiazide	10.0%		
Hydrocortisone		1%	1%
Hydrocortisone acetate		1%	
Hydroxyzine hydrochloride	1.0%		
Ibuprofen	5.0%; 10.0%	5%	
Indomethacin		1%	1%
Kanamycin sulfate	10.0%	10%	10%
Ketoprofen	1.0%	2.5%	
Lamotrigine	10.0%		
Lidocaine	5.0%; 15.0%		
Lidocaine hydrochloride		15%	15%
Mepivacaine hydrochloride		1%	
Metamizol		1%	
Methylprednisolone (aceponate)	1.0%	0.1% alc.	
Metronidazole		1%	1%
Miconazole	1.0% alc.		
Minocycline hydrochloride	10.0%		
Naproxen		5%	
Neomycin sulfate	20.0%	20%	20%
Nitrofurazone	1.0%	1%	1%
Norfloxacin	10.0%		
Nystatin		2%	2%
Olaquindox	1.0%		
Oxytetracycline		3%	3%
Paracetamol (acetaminophen)	10.0% pet.	10%	
Penicillamine	1%		
Phenacetin		10%	
Phenazone		5%	5%
Phenylbutazone	10.0%	10%	10%
Phenylephrine hydrochloride		10% water	10% water
Piperazine		1%	1%
Piroxicam	1.0%	1%	
Polidocanol		3%	3%
Polymyxin B sulfate	5.0%	3%	3%
Potassium clavulanate	10.0%		
Prednisolone		1%	1%
Prilocaine hydrochloride	5.0%		
Pristinamycin	10.0%		
Procaine hydrochloride	1.0%	1%	1%
Promethazine hydrochloride	0.1%	1%; 2%	
Propranolol hydrochloride		2%	
Propyphenazone		1%	
Quinine sulfate	1.0%		
Spiramycin base	10.0%		
Streptomycin sulfate		5%	
Sulfamethoxazole-trimethoprim	10.0%		
Sulfanilamide	5.0%	5%	5%
Tetracycline hydrochloride		1%; 2%	2%
Tobramycin	20.0%	20%	
Triamcinolone acetonide	1.0%	0.1%; 1%	1%
Vancomycin hydrochloride	10.0% water		

The vehicle for all haptens is petrolatum, unless otherwise indicated.

alc., alcohol; Chemotech, Chemotechnique Diagnostics (www.chemotechnique.se); SPCanada, SmartPractice Canada (www.smartpracticecanada.com); SPEurope, SmartPractice Europe (www.smartpracticeeurope.com).

and photoallergic reactions. In some cases, patients have been presensitized to a drug from topical application and develop an exanthema after systemic administration of the drug or a cross-reacting chemical, which is called systemic allergic dermatitis or systemic contact dermatitis. It may present with diverse manifestations, including extensive eczematous dermatitis, maculopapular eruptions, SDRIFE, formerly (and also sometimes today by some authors) called

the baboon syndrome, urticaria, and reactivation of previous eczema or positive patch tests. The severe cutaneous adverse drug reactions (SCARs) are acute generalized exanthematous pustulosis (AGEP), DRESS/DIHS, SJS/TEN, generalized bullous fixed drug eruption, and the hypersensitivity syndrome caused by the antiviral drug abacavir. Excellent reviews of the classification of cutaneous manifestations of drug hypersensitivity and how to diagnose the diseases have recently been published.[2,4,19,20]

Procedure

Consensus-based recommendations for conducting patch testing in patients with (suspected) delayed-type hypersensitivities have been published and should be followed unless otherwise indicated.[29–31] The patch tests should preferably be performed not sooner than 6 weeks and not later than 6 months after the resolution of the adverse skin reaction.[7,20,30] In the case of DRESS/DIHS (in which viruses often play a role), it is advised to wait 6 months after disappearance of the skin exanthema and other sequelae, to avoid any virus reactivation.[5,7,30] The patch test materials should be removed after 2 days, and the reactions read 30 minutes later; a second reading at D3 or D4 is necessary, and a later reading at D7 (or D8–D10) is strongly recommended, the latter especially for corticosteroids (due to the anti-inflammatory effect of the molecule), iodinated contrast media, heparins,[30] and aminoglycoside antibiotics.[32–34] Test reading is usually performed according to the ESCD guidelines for conducting patch tests (at least in Europe).[29]

Tape stripping the test site before the application of test allergens can increase the test's sensitivity. Strip patch testing is recommended in cases in which the results of a previous conventional patch test are suspected to be false-negative or when testing allergens characterized by poor penetration of the corneal layer, such as heparins and aminoglycoside antibiotics. A validated protocol for the performance of tape stripping has been developed.[31]

In cases of fixed drug eruptions, the patches should be applied both to previously affected (postlesional) and to healthy unaffected skin; the tests are usually positive on postlesional skin only. The use of dimethyl sulfoxide as penetration-enhancing vehicle or ethanol may sometimes be useful and result in positive reactions when patch tests with the drug in petrolatum were negative.[35] Single or repeated open tests on postlesional skin with the suspected drugs have also been successful in cases of fixed drug eruptions,[36–40] sometimes even when closed patch tests were negative.[41] In one case, a patch test in a case of SJS/TEN was positive on previously affected skin only.[42] In AGEP, positive patch tests often mimic the clinical picture and show multiple small pustules.

The relevance of any positive drug patch test should be carefully assessed.[43,44] A positive patch test result can help to confirm a possible culprit drug and mostly abolishes the need for further diagnostic testing. However, it must be stressed that a negative patch test result does not exclude the drug tested as the one or one of the chemicals responsible for the observed CADR. With negative patch test results, further diagnostic tests are necessary (the second step usually being an intradermal test with delayed readings).

Drug Patch Test Materials

Approximately 90 drugs used systemically are commercially available for patch testing, and they can be used in cases of suspected CADRs to these drugs (Table 2). For other drugs, pure materials are often not readily available. Therefore, the commercial drugs used by the patients are usually prepared for patch tests, often pulverized tablets. Formerly, a concentration of 30% pet. for all drugs has been recommended,[45] but this resulted in strongly varying concentrations of the active material. These ranged from 0.05% to 30%, with 25% of the drug patch tests having an active ingredient concentration of less than 2% and 25% of >16%.[46] Despite this, this method, in a small study, was shown to be as reliable as patch testing with pure drugs tested at 10% pet.[47]

Nevertheless, preferably, the pure drugs, not the commercialized tablets used by the patients, should be tested, also in order to avoid false-positive results (ie, not indicating hypersensitivity to the active drug material) due to hidden additives in the drug formulations, degradation products, or impurities.[44,48] Most pure systemic drugs can be tested at 10% pet. When the pure chemical is not available, the test material can best be prepared from intravenous powder, the content of capsules, or—when also not available—from powdered tablets to achieve a final concentration of the active drug of 10% pet. wt/wt. When possible, the excipients of the pharmaceutical should also be patch tested. Alternatively, combined commercial drug and pure drug testing may point at either excipients or the active drug being the sensitizer.

TABLE 3. Drugs That Have Reproduced the CADR by Patch Testing

Acyclovir[14]
Amikacin[63]
Amoxicillin[64]
Carbamazepine[65,66]
Clindamycin[67]
Clobazam[68]
Deflazacort[69]
Ethambutol[46]
Hydroxyzine[14]
Isoniazid[46]
Metamizole[70]
Mitomycin C[71]
Paracetamol (acetaminophen)[72]
Piperacillin[73]
Pristinamycin[9,52]
Pseudoephedrine[71,74–76]
Pyrazinamide[46]
Ranitidine[77]
Rifampicin[46,78]
Sodium valproate[79]
Triamcinolone[14]

TABLE 4. Drugs That Have Caused Maculopapular Eruptions and Showed a Positive Patch Test*

Acetaminophen
Acetazolamide
Acexamic acid
Acyclovir
Alendronate
Ambroxol
Aminocaproic acid
Amitriptyline
Amlexanox
Amoxicillin
Amoxicillin-clavulanic acid
Ampicillin
Azathioprine
Aztreonam
Bacampicillin
Benznidazole
Benzylpenicillin
Betamethasone
Captopril
Carbamazepine
Cefalexin
Cefazolin
Cefcapene pivoxil
Cefonicid
Cefoxitin
Ceftriaxone
Cefuroxime
Celecoxib
Cetirizine
Chlorambucil
Chloramphenicol
Cimetidine
Ciprofloxacin
Clavulanic acid
Clindamycin
Clobazam
Clofazimine
Clonidine
Clopidogrel
Clorazepate
Codeine
Deflazacort
Dexamethasone
Dexamethasone sodium phosphate
Diclofenac
Dicloxacillin
Dihydrocodeine
Diltiazem
Enoxaparin
Ephedrine
Eslicarbazepine
Ethambutol
Fenofibrate
Fl(ucl)oxacillin
Fluconazole
Flurbiprofen
Gabapentin
Gadobutrol
Garenoxacin
Heparin
Hydroxyzine
Ibandronic acid
Imipenem
Iobitridol
Iodixanol
Iohexol
Iomeprol
Iopromide
Ioxaglic acid
Ioxitalamic acid
Irbesartan
Isoniazid
Isotretinoin
Lamotrigine
Lansoprazole
Levofloxacin
Lidocaine
Meprobamate
Meropenem
Metamizole
Methylprednisolone
Methylprednisolone hemisuccinate
Metronidazole
Mexiletine
Miconazole
Mirtazapine
Morphine
Nadroparin
Nevirapine
Nimodipine
Norfloxacin
Nystatin
Omeprazole
Oxcarbazepine
Paracetamol
Penicillin V
Phenethicillin
Phenindione
Phenobarbital
Phenylbutazone
Phenytoin
Piperacillin
Piperazine
Practolol
Prednisolone
Prednisone
Pregabalin
Pristinamycin
Proguanil
Pseudoephedrine
Rosuvastatin
Sertraline
Sildenafil
Spiramycin
Sulfamethoxazole-trimethoprim
Terbinafine
Tetrazepam
Thioctic acid
Triamcinolone
Valdecoxib
Valproic acid
Vancomycin
Zinc acexamate

*Details and references can be found in the study of De Groot.[6]

TABLE 5. Drugs That Have Caused Erythroderma, Extensive/Generalized Erythema, or Exfoliative Dermatitis and Showed a Positive Patch Test*

Erythroderma or extensive/generalized erythema
Acetaminophen
Alendronate
Aminophylline
Amoxicillin
Bacampicillin
Betamethasone
Betamethasone sodium succinate
Captopril
Carbamazepine
Ceftazidime
Cefuroxime
Chlorambucil
Chlorpheniramine
Clavulanic acid
Codeine
Cyanamide
Dexamethasone sodium phosphate
Diltiazem
Doxycycline (from photoallergy)
Ephedrine
Flavoxate
Gentamicin
Gliclazide
Hydrocortisone sodium phosphate
Indeloxazine
Iodixanol
Iohexol
Metamizole
Methylprednisolone acetate
Methylprednisolone hemisuccinate
Mexiletine
Pantoprazole
Paracetamol
Paramethasone
Phenylbutazone
Piperacillin
Piperazine
Piritramide
Prednisone
Pristinamycin
Pseudoephedrine
Talastine
Tetrazepam
Vancomycin

Exfoliative dermatitis
Carbamazepine
Chlorambucil
Cloxacillin
Codeine
Dexamethasone
Diltiazem
Lamotrigine
Phenobarbital
Ranitidine

*Details and references can be found in the study of De Groot.[6]

TABLE 6. Drugs That Have Caused AGEP and Showed a Positive Patch Test*

Acetaminophen	Celecoxib	Ibuprofen	Nifuroxazide
Acetazolamide	Cetirizine	Iobitridol	Nimesulide (ALEP)
Acyclovir	Chloramphenicol	Iodixanol	Nystatin
Amoxicillin	Ciprofloxacin	Iohexol	Oxacillin
Amoxicillin-clavulanic acid (AGEP and ALEP)	Clavulanic acid	Iomeprol (AGEP and ALEP)	Paracetamol
	Clindamycin	Iopamidol	Phenobarbital
Ampicillin	Cloxacillin	Iopromide	Prednisolone
Apronalide (allylisopropylacetylurea)	Dalteparin	Ioversol	Prednisolone sodium succinate
Bacampicillin	Dexamethasone sodium phosphate	Isoniazid	Prednisolone sodium tetrahydrophthalate
Beclomethasone	Dextropropoxyphene	Labetalol	
Bemiparin (ALEP)	Dicloxacillin	Lansoprazole	Prednisone
Bendamustine	Diltiazem	Levofloxacin	Pristinamycin
Benznidazole	Enoxaparin	Lincomycin	Propacetamol
Benzylpenicillin	Eperisone	Metamizole	Propicillin
Betamethasone sodium phosphate	Eprazinone	Methoxsalen	Pseudoephedrine
Bleomycin	Ertapenem	Methylprednisolone acetate/hemisuccinate	Ranitidine
Buphenine (nylidrin)	Erythromycin		Spiramycin
Bupropion	Etoricoxib	Metronidazole (AGEP and ALEP)	Terbinafine
Carbimazole	Fl(ucl)oxacillin	Mexiletine	Tetrazepam
Cefixime	Fluconazole	Miconazole	Ticlopidine
Cefotaxime	Fluindione	Mifepristone	Vancomycin
Cefpodoxime	Gadobutrol	Minocycline	Varenicline
Ceftriaxone	Hydroquinidine	Morphine	
Cefuroxime	Hydroxychloroquine		
	Hydroxyzine		

**Details and references can be found in the study of De Groot.*[6]

AGEP, acute generalized exanthematous pustulosis; ALEP, acute localized exanthematous pustulosis.

When the content of the active drug is too low in the patient's drug to achieve a 10% concentration, the whole powder should be diluted in pet. at 30%, which is nonirritant for nearly all commercial medications.[49] Positive patch test results obtained with these in-house preparations should nevertheless always be validated with controls (patch tests with the same materials should be negative in 10–20 nonexposed individuals to exclude irritancy of the patch test material).[29] Heparins/heparinoids, local anesthetics, and iodinated contrast media can be tested as commercial preparations, undiluted.[3] Petrolatum is usually suitable as vehicle. Petrolatum is also the vehicle for the commercially available systemic corticosteroids, but these drugs may be better tested 0.1% and 1% in 70% alcohol to avoid false-negative reactions.

Sensitivity

There can be no doubt that patch testing is a very valuable diagnostic technique in patients with delayed drug eruptions. However, in some of these, its sensitivity is limited, only a minority of the tests being positive. The rates of positive patch test reactions in various investigations have varied widely, depending *inter alia* on the nature of the drug reaction and the drugs involved (Table 1). Some drugs

TABLE 7. Topical Drugs That Have Caused Systemic Allergic Dermatitis[80,81]*

Acetarsone	Clonidine	Iodine	Phenylephrine
Amlexanox	Dibucaine (allergic and photoallergic)	Iodoquinol	Piperazine
Bacitracin	Diltiazem	Lidocaine	Prednisolone acetate
Benzydamine (photoallergic)	Dimethindene	Methyl aminolevulinate	Promestriene
Budesonide	Dorzolamide	Methylphenidate	Pyrazinobutazone
Bufexamac	Ephedrine	Neomycin	Sisomicin
Buprenorphine	Estradiol	Nicotine	Stannous fluoride
Carbarsone	Eucaine	Nifuroxime	Testosterone
Chloral hydrate	Framycetin	Nylidrin	Tetracaine
Chloramphenicol	Gentamicin	Nystatin	Triamcinolone acetonide
Chlorquinaldol	Hydrocortisone aceponate	Oxyphenbutazone	Trimebutine
Clioquinol		Phenylbutazone	

**Details and references can be found in the study of De Groot.*[6]

TABLE 8. Systemic Drugs That Have Caused Systemic Allergic Dermatitis*

Acetaminophen	Dexamethasone	Iodoquinol	Promazine (photosensitivity)
Acyclovir	Dexamethasone disodium phosphate	Isoxsuprine	Promethazine
Alprenolol	Dexketoprofen (photosensitivity)	Ketoconazole	Propacetamol
Aminophylline	Dimethindene	Ketoprofen	Pseudoephedrine
Amlexanox	Dimethyl sulfoxide	Methoxsalen	Pyrazinobutazone
Amoxicillin	Diphenhydramine	Methylprednisolone	Pyridoxine (vitamin B_6)
Bacampicillin	Disulfiram	Methylprednisolone acetate	Ranitidine
Betamethasone	Doxepin	Methylprednisolone sodium succinate	Ribostamycin
Betamethasone acetate	Ephedrine	Methylprednisolone, unspecified salt or ester	Succinylcholine
Betamethasone dipropionate	Epirubicin	Metronidazole	Sulfamethoxazole
Betamethasone sodium phosphate	Erythromycin	Mitomycin C	Sulfanilamide
Carbutamide	Estradiol	Mofebutazone	Sulfathiazole
Cefalexin	Estradiol derivative	Morphine	Terbinafine
Chloral hydrate	Famciclovir	Neomycin	Thiamine (vitamin B_1)
Chloramphenicol	Fenofibrate (photosensitivity)	Nitrofurantoin	Tiaprofenic acid (photosensitivity)
Chlorpheniramine	Fluorouracil	Norfloxacin	Tolbutamide
Chlorpromazine	Framycetin	Nystatin	Tramadol
Chlorquinaldol	Fusidic acid	Oxyphenbutazone	Triamcinolone
Clioquinol	Gentamicin	Phenylbutazone	Triamcinolone acetonide
Clonidine	Hydrocortisone	Piperazine	Trimebutine
Codeine	Hydrocortisone sodium phosphate	Prednisolone	Valaciclovir
Cyanocobalamin	Hydroxyprogesterone	Prednisone	Virginiamycin
Deflazacort	Hydroxyzine	Pristinamycin	
	Ibuprofen	Procaine	

*Details and references can be found in the study of De Groot.[6]

are frequently patch test positive, for example, carbamazepine and some other antiepileptics,[12,50,51] pristinamycin,[52] aminopenicillins,[53] and iodinated contrast media.[12,54] Others, however, give infrequently or hardly ever positive patch tests, including allopurinol. A possible explanation is that the sensitizers are not the drugs themselves, but metabolites, which are not formed in the skin during patch testing. Other important parameters for the sensitivity observed are the patch testing method (often the test was read only once at D2, which will miss a large number of reactions) and the selection of patients for patch testing. When selecting patients with high suspicion of certain drugs having caused a CADR, the frequency of positive results will obviously be higher. In such studies, positive results have been obtained in 43%,[14] 50%,[15] and 32%[16] of the patients tested. In other studies, rates of positive reactions to any CADR were 23%,[12] 23%[50] (children), 25%[8] (many cases of SJS/TEN), 14%[55] (maculopapular eruption, erythroderma, generalized eczema), and 11%[56] and 23%[57] (antibiotics).

Rates of positive reactions reported in specific drug eruptions (not a full literature review) are shown in Table 1. The percentages are very hard (if at all) to compare because of the many different parameters, such as number of studies performed, number of patients investigated, drugs involved, selection of patients, prescription habits, accuracy of clinical diagnosis, patch testing technique, and reading of patch test reactions. However, generally speaking, higher rates of positive reactions may be observed with eczematous eruptions, erythroderma, localized hypersensitivity reactions to subcutaneous injections, maculopapular

TABLE 9. Drugs That Have Caused SDRIFE/Baboon Syndrome (Without Previous Sensitization) and Showed a Positive Patch Test*

Aminocaproic acid	Etoricoxib	Pivampicillin
5-Aminosalicylic acid	Heparin, unfractionated	Prednisolone
Amoxicilllin	Hydroxyzine	Prednisone
Amoxicillin-clavulanic acid	Iomeprol	Pristinamycin
Clarithromycin	Iopromide	Pseudoephedrine
Clindamycin	Itraconazole	Secnidazole
Deflazacort	Metronidazole	Sevoflurane
Etonogestrel	Penicillin V	Tacrolimus

*Details and references can be found in the study of De Groot.[6]

TABLE 10. Drugs That Have Caused SDRIFE/Baboon Syndrome (With Previous Sensitization) and Showed a Positive Patch Test*

Aminophylline	Dexamethasone	Neomycin
Amoxicillin	Hydrocortisone	Nystatin
Betamethasone	Methylprednisolone sodium succinate	Sevoflurane (inhalation)
Cloprednol	Mitomycin C	Terbinafine
Deflazacort		Triamcinolone acetonide

*Details and references can be found in the study of De Groot.[6]

TABLE 11. Drugs That Have Fixed Drug Eruptions and Showed a Positive Patch Test*

Aceclofenac	Citiolone	Ioversol	Phenylephrine
Acetaminophen	Clarithromycin	Lamotrigine	Picosulfuric acid
Acyclovir	Codeine	Levocetirizine	Piroxicam
Adalimumab	Cyclophosphamide	Mefenamic acid	Pristinamycin
Aminophylline	Dimenhydrinate	Meprobamate	Promethazine
Amlexanox	Dipyrone	Mesalazine	Pseudoephedrine
Amoxicillin	Doxycycline	Mesna	Rupatadine
Amoxicillin-clavulanic acid	Ephedrine	Metamizole	Scopolamine
Antipyrine salicylate	Erythromycin	Metronidazole	Sulfadiazine
Apronalide (allylisopropylacetylurea)	Esomeprazole	Naproxen	Sulfamethoxazole
Atenolol	Ethenzamide	Nimesulide	Sulfamethoxazole-trimethoprim (cotrimoxazole)
Atorvastatin	Etoricoxib	Norfloxacin	Tenoxicam
Bromhexine	Feprazone	Ofloxacin	Tetracycline
Carbamazepine	Fluconazole	Ornidazole	Tetrazepam
Carbocysteine	Fulvestrant	Oxcarbazepine	Ticlopidine
Celecoxib	Hydroxyzine	Oxytetracycline	Tosufloxacin tosilate
Cetirizine	Ibuprofen	Paracetamol	Trazodone
Chlormezanone	Iohexol	Pefloxacin	Trimethoprim
Ciprofloxacin	Iomeprol	Pefloxacin	Vinburnine
	Iopamidol	Phenazone	
	Iopromide	Phenobarbital	

**Details and references can be found in the study of De Groot.*[6]

TABLE 12. Drugs That Have Caused Drug Reaction With Eosinophilia and Systemic Symptoms/Drug Hypersensitivity Syndrome (DRESS/DIHS) and Showed a Positive Patch Test*

Abacavir	Clindamycin	Ioxaglic acid	Pristinamycin
Acetaminophen	Clobazam	Ioxitalamic acid	Proguanil
Acetylsalicylic acid	Cloxacillin	Isoniazid	Propylthiouracil
Acyclovir	Codeine	Lamotrigine	Pyrazinamide
Amikacin	Cyanamide	Lansoprazole	Pyrimethamine
Aminosalicylic acid	Dabrafenib	Levofloxacin	Ranitidine
Amoxicillin	Diclofenac	Meropenem	Rifampicin
Amoxicillin-clavulanic acid	Dicloxacillin	Metamizole	Spironolactone
Atovaquone	Diltiazem	Mexiletine	Sulfamethoxazole
Benznidazole	Enoxaparin	Miconazole	Sulfamethoxazole-trimethoprim
Benzylpenicillin	Esomeprazole	Olanzapine	Sulfasalazine (positive photopatch test)
Captopril	Ethambutol	Oxacillin	Teicoplanin
Carbamazepine	Ethosuximide	Oxcarbazepine	Tenoxicam
Cefadroxil	Fl(ucl)oxacillin	Pantoprazole	Tetrazepam
Cefotaxime	Fluindione	Paracetamol	Topiramate
Cefoxitin	Fluvoxamine	Penicillin V	Triazolam
Ceftriaxone	Fusidic acid (or TEN?)	Phenindione (*possibly* DRESS)	Tribenoside
Cefuroxime	Gadobutrol	Phenobarbital	Valaciclovir
Celecoxib	Hydroxychloroquine	Phenytoin	Valproic acid
Chloroquine	Iobitridol	Piperacillin	Vancomycin
Cilastatin, mixture with imipenem	Iodixanol	Piperacillin-tazobactam	Zonisamide
Ciprofloxacin	Iohexol	Potassium aminobenzoate	
Clarithromycin	Iomeprol		
	Iopromide		
	Ioversol		

**Details and references can be found in the study of De Groot.*[6]

TABLE 13. Drugs That Have Caused Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis and Showed a Positive Patch Test*

Aminophenazone	Clindamycin	Lamivudine	Procaine benzylpenicillin
Amoxicillin	Cloxacillin	Lamotrigine	Propranolol
Ampicillin	Diclofenac (doubtful)	Lansoprazole	Pseudoephedrine
Benznidazole	2,3-Dimercapto-1-propanesulfonic acid	Meropenem	Pyrabital
Benzylpenicillin	Emtricitabine	Metamizole	Pyrazinamide
Bortezomib	Erythromycin	Metronidazole	Ramipril
Bromisoval	Esomeprazole	Pantoprazole	Sulfamethoxazole
Bucillamine	Ethosuximide	Penicillin G	Sulfonamide
Carbamazepine	Fexofenadine	Phenobarbital	Terbinafine
Ceftriaxone	Ibuprofen	Phenylbutazone	Tetrazepam
Cefuroxime	Iohexol	Phenytoin	Vancomycin
Chlorambucil	Isoniazid	Pristinamycin	
Chlormezanone			

*Details and references can be found in the study of De Groot.[6]

eruptions, DRESS/DIHS, AGEP, and the abacavir hypersensitivity syndrome. Low rates of positive drug patch tests have been found in patients with SJS/TEN. In the case of DRESS/DIHS, the high percentages may partly be explained by the large number of cases caused by antiepileptics, especially carbamazepine, which are frequently patch test positive. In patients with systemic allergic dermatitis, a (near) 100% rate of positive reactions should be possible as, by definition, presensitization to a topical drug has taken place. For the other drug eruptions, there are not enough data (eg, photoallergic dermatitis), or contradictory results have been obtained. In the case of fixed drug eruptions, for example, rates have ranged from 0% to 79% (Table 1).

Negative Patch Tests

A positive patch test result can help to confirm a possible culprit drug. Unfortunately, a negative patch test does not guarantee that the tested drug was not the cause of the skin reaction. Indeed, not infrequently,

TABLE 14. Drugs That Have Caused Photoallergic Dermatitis and Showed a Positive Photopatch Test*

Acetylsalicylic acid	Diltiazem	Hydroxyurea	Promethazine
Actarit	Diphenhydramine	Ibuprofen (doubtful)	Pyridoxine
Afloqualone	Doxycycline	Isoniazid	Pyritinol
Althiazide (uncertain)	Dronedarone	Isotretinoin (photoaggravation)	Quinidine
Amantadine	Droxicam	Ketoprofen	Quinine
Ambroxol	Efavirenz	Levopromazine	Ramipril
Amitriptyline	Enoxacin	Lomefloxacin	Simvastatin
Amoxicillin	Epirubicin	Mequitazine	Spironolactone (uncertain)
Ampiroxicam	Erlotinib (unconvincing case)	Methoxsalen	Sulfasalazine (photoallergy in DRESS)
Benzydamine	Esomeprazole (unconvincing case)	Methyldopa	Tegafur
Carbamazepine	Etretinate (uncertain)	Naproxen	Tenofovir (uncertain)
Carprofen	Fenofibrate	Nicardipine	Terbinafine
Chloroquine	Flutamide	Paroxetine	Tetrazepam
Chlorpromazine	Fluvoxamine	Pirfenidone	Thioridazine
Ciprofloxacin	Griseofulvin	Piroxicam	Tiaprofenic acid
Clofibrate	Hydrochlorothiazide	Piroxicam betadex	Tilisolol
Clomipramine	Hydroquinidine	Potassium aminobenzoate	Triflusal
Cyamemazine	Hydroxychloroquine	Promazine	Trimeprazine
Dapsone			
Dexketoprofen			

*Details and references can be found in the study of De Groot.[6]

TABLE 15. Drugs That Have Caused Eczematous, Erythema Multiforme-Like or Lichenoid Drug Eruptions or Urticaria and Showed a Positive Patch Test*

Eczematous drug eruption

Amlexanox	Cyanocobalamin	Hydromorphone	Prednisolone
Amoxicillin	Danaparoid	Hydroxyzine	Pristinamycin
Ascorbic acid	Desloratadine	Interferon (PEG-IFN-α2a)	Pseudoephedrine
Benzylpenicillin	Dexamethasone	Isoniazid	Streptomycin
Bupivacaine	Dexamethasone phosphate	Lidocaine	Succinylcholine
Captopril	Dipyridamole	Metamizole	Tacrolimus
Carbamazepine	Disulfiram	Methoxsalen	Tamsulosin
Carbimazole	Enoxaparin	Nadroparin	Tobramycin
Cefazolin	Epirubicin	Nimodipine	Triamcinolone
Cetirizine	Ethambutol	Penicillin G	Triflusal (UVB aggravated)
Clomipramine (+photoallergy)	Heparin, unfractionated	Phenobarbital	
Codeine		Pravastatin	

Erythema multiforme-like drug eruption

Acetaminophen	Clindamycin	Pancreatin	Sildenafil (uncertain)
Amoxicillin (also in amoxicillin-clavulanic acid)	Diltiazem	Paracetamol	Sorafenib
Carbamazepine	Hydroxyzine	Paroxetine (photosensitive)	Sulfaguanidine
Ceftriaxone	Iohexol	Phenazone	Tetrazepam
Cefuroxime	Iopamidol	Phenytoin	Tobramycin
Celecoxib	Mepivacaine	Prasugrel	Triamcinolone acetonide
Chlorambucil	Methotrexate	Prednisone	Tribenoside
	Naproxen (photosensitive)	Risedronic acid	

Lichenoid drug eruption

Acetazolamide	Captopril	Cycloserine	
Aminophylline	Carbamazepine	Tiopronin	

Urticaria/urticarial exanthema/urticaria-like exanthema

Acyclovir	Ciprofloxacin	Interferon (PEG-IFN-α2a)	Nicomorphine
Aminophylline	Clavulanic acid	Iohexol	Oxcarbazepine
Amoxicillin	Clofazimine	Iopamidol (uncertain)	Omeprazole
Ampicillin	Codeine	Lidocaine	Penicillin G
Bacampicillin	Deflazacort	Methylprednisolone acetate	Piperazine
Benznidazole	Dexamethasone	Methylprednisolone hemisuccinate	Pristinamycin
Benzylpenicillin	Diclofenac		Tetrazepam
Ceftriaxone	Hydrocortisone sodium phosphate		
Cefuroxime			

**Details and references can be found in the study of De Groot.*[6]

TABLE 16. Bullous Eruptions*

Allopurinol	Papular exanthema with bullae
Amoxicillin	Bullous exanthema/erythema multiforme
Amoxicillin-clavulanic acid	Linear IgA disease; bullous exanthema
Benzylpenicillin (penicillin G)	Bullous exanthema/erythema multiforme; bullous pemphigoid
Ceftriaxone	Linear IgA bullous dermatosis; bullous exanthema/erythema multiforme
Metronidazole	Linear IgA bullous dermatosis; bullous exanthema/erythema multiforme; erythematous, partly urticarial exanthema with bullae
Penicillin V	Bullous pemphigoid
Sulfamethoxazole	Bullous drug eruption; bullous exanthema/erythema multiforme; maculopapular eruption with vesicles and bullae

**Details and references can be found in the study of De Groot.*[6]

TABLE 17. Allergic Reactions to Injections (Except Intravenous)*

Drug	Clinical Description/Diagnosis
Articaine	Localized eczematous reaction from subcutaneous injection
Bemiparin	Localized eczematous plaques at the injection sites
Bupivacaine	Localized allergic reaction to subcutaneous injection
Certoparin	Localized eczematous plaques at the injection sites
Dalteparin	Localized eczematous plaques at the injection sites
Danaparoid	Localized eczematous plaques at the injection sites
Dutasteride	Angioedema-like contact dermatitis caused by mesotherapy
Enoxaparin	Localized eczematous plaques at the injection sites
Gentamicin	Localized allergic dermatitis from intra-articular injection
Heparin, unfractionated	Generalized delayed-type skin reaction; erythema on both hands; local and generalized vesiculopustular eruption; erythematous and eczematous plaques at the injection sites
Hydromorphone	Localized allergic reaction from subcutaneous infusion; generalized dermatitis
Interferon	Localized allergic reaction at the injection site
Lidocaine	Localized allergic reaction (from subcutaneous injection); micropapular eruption; generalized vesiculobullous exanthema; urticaria-like exanthema
Mepivacaine	Localized allergic reaction (from subcutaneous injection); localized maculopapular rash from sclerotherapy (intravenous injection)
Methylprednisolone acetate	Unspecified and localized skin eruption from intra-articular injection; chronic urticaria from combined immediate- and delayed-type hypersensitivity; localized allergic reactions after retrobulbar injections
Nadroparin	Localized eczematous plaques at the injection sites
Paramethasone	Localized allergic reaction from intralesional injections
Prednisolone acetate	Local allergic reaction from intra-articular injection
Prilocaine	Localized allergic reactions from subcutaneous/mucosal injections
Procaine	Localized allergic reactions from subcutaneous/mucosal injections; exanthemas
Secukinumab	Localized and expanding eczematous reaction from subcutaneous injection
Tinzaparin	Localized eczematous plaques at the injection sites
Triamcinolone acetonide	Localized allergic reaction from intralesional injection; reactions to intra-articular injections: erythema multiforme-like allergic dermatitis, morbilliform and partially persistent urticarial dermatitis, localized and generalized allergic reaction, and generalized erythema

**Details and references can be found in the study of De Groot.*[6]

oral provocation tests or unintentional repeated exposure to patch test–negative drugs have caused a recurrence of the CADR.[58,59] In the same manner, negative reactions to drugs patch tested in the search for safe alternatives do not guarantee that there will be no adverse reaction when the drug is administered, especially with chemically similar, potentially cross-reacting pharmaceuticals.

When patch tests are negative, intradermal tests with late readings at D2 and D3/D4 may be clearly positive, thus identifying both the causative drug and the delayed-type hypersensitivity mechanism involved.[45,60–62] In fact, intradermal tests are generally more sensitive than patch tests.[7] Intradermal testing with corticosteroids may reveal additional sensitizations not picked up by patch tests, especially in the case of hydrocortisone, which is frequently false-negative in the patch test. However, notably with the stronger corticosteroids, there is a risk of skin atrophy if used in (too) high concentrations.[32–34]

Safety

Patch tests with drugs are—also in the SCARs—a low-risk method of diagnostic testing, because they can reproduce delayed-type hypersensitivity to drugs with a moderate exposure of the patient to offending drugs. In very infrequent cases, however, patch testing has (mildly or severely) reproduced the drug reaction (Table 3). Still, in some groups, notably patients with human immunodeficiency virus/acquired immune deficiency syndrome, there seems to be a significant risk of generalized systemic reactions after patch testing anti-tuberculosis drugs, in 1 group in 10 of 11 (91%) patch-tested patients.[46] Nevertheless, it is generally accepted that, if necessary with appropriate dose adjustment in the patch, testing is feasible even in the most severe cases of cutaneous drug hypersensitivity, including SJS/TEN.[19,29,30]

DRUGS, DRUG ERUPTIONS, AND POSITIVE PATCH TESTS

In reviewing the literature, the author has found 507 systemic drugs that have caused drug eruptions and/or occupational allergic contact dermatitis confirmed by positive patch tests to the culprit drugs.[6] The former category is shown here in tabular format. Drugs responsible for maculopapular eruptions with a positive patch test are shown in Table 4; those causing erythroderma, extensive/generalized erythema, or exfoliative dermatitis in Table 5; AGEP in Table 6; systemic

TABLE 18. Drugs That Have Caused Any Other Drug Eruption and Showed a Positive Patch Test*

Drug	Clinical Description/Diagnosis
Acetaminophen	Micropapular eruption; generalized pruriginous rash
Allopurinol	Unspecified drug eruption
Aminophylline	Generalized rash consisting of erythematous papules
Amitriptyline	Generalized rash
Amlexanox	Pityriasis rosea-like exanthema
Amoxapine	Erythematous papular eruption on the trunk and limbs
Amoxicillin	Unspecified drug eruption
Ampicillin	Unspecified drug eruption
Apronalide (allylisopropylacetylurea)	Mucocutaneous ocular syndrome
Ascorbic acid	Papular exanthema
Azathioprine	Acneiform eruption
Bacampicillin	Unspecified drug eruption
Benzylpenicillin (penicillin G)	Generalized exanthema with fever; unspecified drug eruption
Betamethasone acetate	Erythema of the face and neck
Betamethasone sodium succinate	Erythema of the face and neck
Bucillamine	Red papules on the face, neck and arms; unspecified drug eruption
Captopril	Erythematous eruption on the cheeks
Carbamazepine	Erythema and edema of the face; "allergic reactions"; unspecified drug eruption
Carbocromen	Erythematous, nonitchy eruption on the face, back, and arms
Carbocysteine	Drug fever (fever without cutaneous eruption)
Carbromal	Purpuric rash
Cefaclor	Unspecified drug eruption
Cefadroxil	Unspecified drug eruption
Cefalexin	Unspecified drug eruption
Cefalotin	Unspecified drug eruption
Cefcapene pivoxil	Pruritic papules and erythema on the trunk and arms
Ceftriaxone	Exanthematous rash; undefined cutaneous eruption; erythematous, partly urticarial exanthema with blisters
Cefuroxime	Unspecified drug eruption
Chloramphenicol	Drug eruption
Chloroquine	Erythematous and mainly papular eruption
Clindamycin	Cutaneous vasculitis
Cloxacillin	Unspecified drug eruption
Clozapine	Erythematous, papular, and pustular eruption with vasculitis
Codeine	Exanthema
Dexamethasone	Exanthema
Diazepam	Eczema of the hands and periorbital edema
Diltiazem	Psoriasiform eruption; generalized demarcated erythema with infiltration all over the body
Dimethindene	Widespread maculopapular and vesicular rash
Emtricitabine	Unspecified exanthema with palpebral edema
Ephedrine	Itchy dermatosis
Ethambutol	Desquamative, erythematous, papular rash, with painful crusts and excoriations, spreading from the face and hands to the rest of the body
Gabexate	Panniculitis with eosinophilic infiltration from intravenous administration
Gentamicin	Unspecified drug eruption
Indeloxazine	Eosinophilic pustular folliculitis (Ofuji disease) (atypical)
Iodixanol	Erythema and deep edema
Iohexol	Facial edema and respiratory distress
Isoniazid	Desquamative, erythematous, papular rash, with painful crusts and excoriations, spreading from the face and hands to the rest of the body; unspecified drug reaction
Lansoprazole	Maculopapular dermatitis and dyspnea
Levocetirizine	Multiple itchy, erythematous, and edematous plaques
Magnesium oxide	Erythematous eruption on the abdomen and back (uncertain)
Meprobamate	Anaphylactoid reaction with cyanosis, dyspnea, circulatory failure, and maculopapular eruption

(Continued on next page)

TABLE 18. *(Continued)*

Drug	Clinical Description/Diagnosis
Meropenem	Unspecified drug eruption
Metamizole	Diffuse edema of the face with breathing difficulty; widespread pruritic exanthema
Methyldopa	Generalized polymorphic eruption with excoriated papulovesicular lesions, plaques of nummular dermatitis, and bullae on the palms and soles
Methylprednisolone hemisuccinate	Generalized skin rash; generalized erythema, urticaria, and dyspnea
Methylprednisolone sodium succinate	Widespread macular exanthema succinate
Metoprolol	Psoriasiform dermatitis
Mexiletine	Generalized pruritic eruption with papules, infiltrated erythematous patches and pustules
Nadroparin	Spreading of itchy erythematous plaques over the trunk
Nebivolol	Periorbital eczema
Nystatin	Generalized micropapular eruption with edema of the face; erythematous macules on the abdomen and thighs and eczema of a hand
Oxcarbazepine	Unspecified skin reaction
Oxycodone	Exanthema
Penicillin V	Unspecified drug eruption
Pheniramine	Urticarial and maculopapular eruption
Phenobarbital	Unspecified drug eruption
Phenytoin	EMPACT (erythema multiforme associated with phenytoin and cranial radiation therapy); unspecified drug eruption
Piroxicam	Acrovesicular (dyshidrosiform) dermatitis
Prednisolone	Pustular exanthema; generalized rash
Propylthiouracil	Leukocytoclastic vasculitis
Pseudoephedrine	Generalized papulovesicular eruption with mucosal involvement; recurrent erythema; generalized pruritic exanthematous eruption; pigmented purpuric dermatosis
Pyrazinamide	Pruriginous rash mainly on the thorax and abdomen
Streptomycin	Toxic erythema with generalized follicular pustules, later developing into spinous protrusions
Sulfamethoxazole	Unspecified exanthema
Sulfamethoxazole-trimethoprim	Unspecified eruption
Tenofovir	Unspecified exanthema with palpebral edema
Terfenadine	Unspecified drug exanthema
Tetrazepam	Papular and micropapular exanthema
Topiramate	Erythema of the neck, nausea, vomiting

**Details and references can be found in the study of De Groot.*[6]

allergic dermatitis from topical drugs in Table 7 and from systemic drugs in Table 8; SDRIFE/baboon syndrome without previous sensitization in Table 9; SDRIFE/baboon syndrome with previous sensitization in Table 10; fixed drug eruption in Table 11; DRESS/DIHS in Table 12; SJS/TEN in Table 13; photoallergic dermatitis in Table 14; eczematous, erythema multiforme-like, and lichenoid drug eruptions or urticaria in Table 15; bullous eruptions in Table 16; allergic reactions to injections (except intravenous) in Table 17; and drugs that have caused any other drug eruption (with specification of their nature) in Table 18.

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