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REVIEW

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Results of patch testing in acute generalized exanthematous pustulosis (AGEP): A literature review

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Abstract

The literature on positive patch-test results in acute generalized exanthematous pustulosis (AGEP) is reviewed. Ninety-three drugs were identified that have together caused 259 positive patch tests in 248 patients with AGEP. The drug classes causing the highest number of reactions are beta-lactam antibiotics (25.9%), other antibiotics (20.8%), iodinated contrast media (7.3%), and corticosteroids (5.4%), together accounting for nearly 60% of all reactions. The highest number of reactions to individual drugs was to amoxicillin (n = 36), followed by pristinamycin (n = 25), diltiazem (n = 14), amoxicillin-clavulanic acid (n = 13), clindamycin (n = 11), and iomeprol (n = 8); 59 of the 93 drugs each caused a single case only. The "Top-10" drugs together caused over 50% of all reactions. The sensitivity of patch testing (percentage of positive reactions) in patients with AGEP is largely unknown, but may generally be ~50%, which also applies to pristinamycin. Patch testing in AGEP appears to be safe, although mild recurrence of AGEP skin symptoms or other rashes may occur occasionally. Clinical aspects of AGEP, including epidemiology, etiology and pathophysiology, clinical features, histology, treatment, and prognosis are briefly presented, as are diagnosing the disease and identifying the culprit drugs with patch tests, intradermal tests, in vitro tests, and challenge tests.

KEYWORDS
acute generalized exanthematous pustulosis, amoxicillin, beta-lactam antibiotics, delayed-type hypersensitivity, diltiazem, iodinated contrast media, positive patch tests, pristinamycin

1 | INTRODUCTION

Acute generalized exanthematous pustulosis (AGEP) belongs—together with drug reaction with eosinophilia and systemic symptoms (DRESS),[1] Stevens-Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), and generalized bullous fixed drug eruption—to the severe cutaneous adverse reactions (SCARs). In its characteristic form, AGEP manifests with rapid development of widespread nonfollicular, sterile pustules on an erythematous base accompanied by fever (temperature >38.0°C), leukocytosis, elevated levels of C-reactive protein (CRP), and mostly increased levels of neutrophils.[2,3] There are strong indications that delayed-type (type IV) hypersensitivity plays an important role in its pathophysiology, including the finding of positive patch tests, positive delayed intradermal tests, and positive lymphocyte transformation tests in response to (suspected) culprit drugs and the demonstration of drug-specific T cells in patients with AGEP.[2,4]

This article provides a review of reported positive drug patch tests in patients diagnosed with AGEP. The aims of the literature study were to find answers to the following questions: (1) which drugs have induced positive patch tests in patients with AGEP; (2) which pharmaceuticals are the most frequent culprits; (3) what is the sensitivity of patch testing (percentage of positive reactions) when testing groups of patients with AGEP and when testing specific drugs; (4) is there evidence for optimal patch-test concentrations and vehicles; and (5) how safe is patch testing in AGEP? In addition, the study aimed at providing an extensive bibliography of the available relevant

literature for current and future reference for the readers of *Contact Dermatitis*.

To this end, a literature review was performed of positive patch tests in patients with AGEP by searching PubMed/MEDLINE, EMBASE, and SCOPUS with no time limit. Search terms were "AGEP" and "acute generalized exanthematous pustulosis" for PubMed/MEDLINE; these terms were combined with "patch test" for searching in EMBASE and SCOPUS. All articles found and relevant references in their literature lists (and in the literature lists of these secondary articles, and so on) were screened for positive results of patch tests. Much relevant information (including articles not found by these searches) had already been identified while the author was searching data for his book *Monographs in contact allergy*, *Volume 4*, *Systemic drugs*, both data for AGEP and for other subjects of the book (using multiple, unrelated search terms). Details of case reports on AGEP and positive patch tests can be found in that publication.[5]

Because AGEP is a very infrequent drug reaction and, consequently, not all readers may be familiar with this severe and potentially life-threatening disease, some general information on AGEP (largely based on review articles to limit the already vast number of references) is given first before providing and discussing the data found in literature on positive patch tests in AGEP.

2 | ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

2.1 | General introduction

Acute generalized exanthematous pustulosis (or AGEP) is a severe cutaneous reaction pattern characterized by the rapid development of nonfollicular, sterile pustules on an erythematous base accompanied by fever. The disease is most frequently caused by drugs, notably antibiotics. AGEP was originally considered to be a form of pustular psoriasis; in 1968, it was first suspected that it was actually a separate entity.[6] The name "acute generalized exanthematous pustulosis" (or actually "pustulose exanthématique aiguë généralisée (PEAG)" was proposed to describe the disease in 1980 in a French publication.[7] In this article, the most important practical aspects of AGEP are presented, but it falls outside its scope to provide a detailed discussion. Recent review articles, sometimes combined with other SCARs, can be found in refs.[2, 4, 8–14] (focus on epidemiology),[15-17] (focus on pathophysiology, differential diagnoses and culprit drugs), and.[18]

2.2 | Epidemiology

AGEP is a rare adverse drug reaction with an incidence of one to five cases per million per year, but it might be underreported. It can occur at any age (mean age in one large study: 56 years [range 4-91 years]) and seems to be more frequent (80%) in women.[18,19] As pristinamycin is a very frequent cause, AGEP is seen more often in some European countries, where this antibiotic is widely used, notably in France.[10]

2.3 | Etiology and pathophysiology

The exact pathophysiology of AGEP is unknown, but it is generally regarded as a T cell–mediated hypersensitivity reaction with a sterile neutrophilic inflammatory response, mostly to drugs.[4] This concept is supported by positive patch tests, positive delayed intradermal tests, and positive in vitro tests in response to culprit drugs.[2,4] Models that have been proposed to explain the interactions between drugs or metabolites and immunological synapses leading to sensitization have been discussed by the author recently.[1]

AGEP is in over 90% of the patients an adverse reaction to drugs, especially pristinamycin (mostly used in France), aminopenicillins (amoxicillin and ampicillin), quinolones, sulfonamides, chloroquine and hydroxychloroquine, terbinafine, diltiazem, ketoconazole, and fluconazole.[19] The literature provides a long list of single case reports and case series in which a large number of different drugs are documented as potential triggers (Table 1; only drugs are included those that have caused AGEP and showed a positive patch test to the culprit drug[s]). All drugs that have caused AGEP published before 2010 (not selected for positive patch tests), have been reviewed in ref.[17]

In some cases, AGEP has been reported as the result of bacterial, viral, or parasitic infections,[4,15] although the EuroSCAR group did not find a relevant association with infections.[19] Spider bites, herbal medications, *Rhus* (lacquer), contact allergy to mercury and topical drugs[18] and psoralen-UVA (PUVA) treatment have apparently induced AGEP and venoms, foods, and xenobiotics have also been suspected to do so. Sometimes AGEP is idiopathic: no cause/trigger can be found.[4,15]

2.4 | Clinical features

AGEP is clinically characterized by the rapid development of tens to hundreds small, sterile, nonfollicular pustules on an erythematous edematous base, which can lead to erythroderma.[9] It starts and is accentuated in the main folds (axillary, inguinal, and submammary areas) and spreads within a few hours on the trunk, arms, and legs.[2,4] The palms and soles are rarely affected. During the early stage, pustule confluence can result in a positive Nikolsky sign, with superficial skin detachment.[9,12] Characteristic for AGEP is the collaret-shaped desquamation of these pustules in the healing phase.[15] Additional skin symptoms can comprise edema of the face and unspecific lesions such as purpura, "atypical" targets, blisters, or vesicles.[4,19] There is an itching or sometimes burning sensation. Mucous membrane involvement is present in <20% of cases, usually mild, and is in general restricted to one site, mostly oral.[9,19] Sometimes patients have lymphadenopathy.

Systemic inflammation signs in the acute phase of the disease include fever (temperature >38.0°C), leukocytosis (white blood cell count [WBC] >10 000/mL), elevated levels of C- reactive protein (CRP), and mostly increased levels of neutrophils (>7000/mL).[2,4] Thirty percent of the patients present an eosinophilia and in 75% of cases hypocalcemia, probably related to hypoalbuminemia, is found.[4]

TABLE 1 Drugs that have caused acute generalized exanthematous pustulosis (AGEP) and showed a positive patch test

Category	Drugs
Antibiotics	
Beta-lactams	Amoxicillin, amoxicillin-clavulanic acid, ampicillin, ampicillin-cloxacillin, ampicillin-sulbactam, bacampicillin, benzylpenicillin, cefixime, cefotaxime, cefpodoxime, ceftriaxone, cefuroxime, clavulanic acid, cloxacillin, dicloxacillin, ertapenem, floxacillin (flucloxacillin), oxacillin, propicillin
Fluoroquinolones	Ciprofloxacin
Macrolides	Erythromycin, pristinamycin, spiramycin, virginiamycin
Other antibiotics	Chloramphenicol, clindamycin, isepamicin, lincomycin, minocycline, nifuroxazide, vancomycin
Antiepileptic drugs	Carbamazepine, phenobarbital
Antifungal/antiviral drugs	Acyclovir, fluconazole, miconazole, nystatin, terbinafine
Antihistamines	Cetirizine, hydroxyzine, ranitidine
Antiparasitic drugs	Benznidazole, metronidazole
Corticosteroids	Beclomethasone, betamethasone sodium phosphate, dexamethasone sodium phosphate, methylprednisolone acetate or hemisuccinate, prednisolone, prednisolone sodium succinate, prednisolone sodium tetrahydrophthalate, prednisone
Iodinated contrast media	Iobitridol, iodixanol, iohexol, iomeprol, iopamidol, iopromide, ioversol
NSAIDs/analgesics	Acetaminophen (paracetamol), acetaminophen-dextropropoxyphene, celecoxib, dextropropoxyphene, etoricoxib, ibuprofen, metamizole, morphine, propacetamol
Miscellaneous drugs	Acetazolamide, apronalide (allylisopropylacetylurea), bendamustine, bleomycin, bupropion, carbimazole, codeine, diltiazem, enoxaparin, eperisone, eprazinone, fluindione, gadobutrol, hydroquinidine, hydroxychloroquine, isoniazid, labetalol, lansoprazole, methoxsalen, mexiletine, nylidrin (buphenine), pseudoephedrine, ritodrine, tetrazepam, ticlopidine, varenicline

Note: Adapted from ref.[5]
Abbreviation: NSAID, nonsteroidal anti-inflammatory drug.

In 15% to 20% of the patients, especially elderly individuals,[20] there may be internal organ involvement, notably hepatic, renal, and pulmonary dysfunction. Hepatic involvement may present as elevated liver enzymes, steatosis, or hepatomegaly.[4,21] Pulmonary involvement includes bilateral pleural effusion resulting in hypoxemia, requiring supplemental oxygen. Multiple organ dysfunction in AGEP may occasionally require treatment in an intensive care unit.[21]

The time period from drug ingestion to reaction onset ranges from several hours to 11 days, but is usually within 48 hours, with antibiotics having a median of 24 hours. In these "acute" cases, previous sensitization to the drug must have occurred,[17] but in the majority of these patients, evidence for such a prior exposure cannot be found.[15]

2.5 | Histology

AGEP is characterized histologically by intracorneal, subcorneal, and/or intraepidermal pustules with papillary dermal edema containing neutrophilic and eosinophilic infiltrates, accentuated around the vessels, and occasionally extravasated erythrocytes. The majority of intraepidermal pustules are located in the upper epidermis, often contiguous with the subcorneal pustules. The pustules tend to be large and contain eosinophils. Spongiform changes may be observed in the intra- and subcorneal pustules. Epidermal changes also include spongiosis with exocytosis of neutrophils and necrotic keratinocytes.[2,22] No significant association has been established between AGEP and pustular psoriasis.[2,22] The histology of AGEP reveals larger eosinophil infiltrates, more necrotic keratinocytes, and larger mixed dermal and interstitial infiltrates than in pustular psoriasis, and the absence of dilated blood vessels.[9,23] Pustular psoriasis typically shows, besides microabscesses, prominent epidermal psoriatic changes such as papillomatosis and acanthosis.[16,23]

2.6 | Diagnosis

2.6.1 | Diagnosing AGEP

The diagnosis of AGEP is based on clinical and histological criteria. An AGEP validation score has been developed by the EuroSCAR group. This is a standardized scheme based on morphology, clinical course, and histology that classifies patients with suspected AGEP as having definite, probable, possible, or no AGEP[24] (Table 2).

The differential diagnosis consists primarily of generalized pustular psoriasis (which does not heal quickly as AGEP does after removing the culprit medication), but other conditions, such as subcorneal pustular dermatosis, Sweet's syndrome, bacterial and fungal folliculitis (candidiasis), bullous impetigo, staphylococcal scalded skin syndrome, pustular vasculitis, and varicella should be considered.[4,12,17,20] Numerous micropustules may also be seen in DRESS, but these are often follicular.[20] Overlap forms of AGEP with DRESS and TEN have been described.[4]

2.6.2 | Diagnosing the culprit drug(s)

Patch tests

Patch testing with all drugs, which should be performed no sooner than 6 weeks after complete recovery, is useful, especially to identify the cause of AGEP when the responsible drug is unclear (many drugs used) and to confirm the suspected causality of a drug.[25,26,27] The

TABLE 2 Diagnostic criteria of acute generalized exanthematous pustulosis (AGEP)

Features of AGEP	Absent	Present/yes	Typical
Exanthema			
Pustules	0	1	2
Erythema	0	1	2
Distribution pattern	0	1	2
Collaret-shaped postpustular desquamation	0	1	
Course			
Mucosal involvement	0	−2	
Acute onset ≤10 days	−2	0	
Resolution ≤15 days	−4	0	
Fever, temperature ≥38°C	0	1	
Neutrophilia ≥7000/mm^3	0	1	
Histology			
Other diagnosis	0	−10	
Histology not typical or not performed	0	0	
Exocytosis of peripheral neutrophils	0	1	
Subcorneal and/or intraepidermal non-spongiform pustules or pustules not further specified with papillary edema or subcorneal and/or intraepidermal spongiform pustules or pustules not further specified without papillary edema	0	2	
Spongiform subcorneal and/or intraepidermal pustules	0	3	
Final score			
≤0 Not AGEP			
1-4 Possible case of AGEP			
5-7 Probable case of AGEP			
8-12 Definite case of AGEP			

Note: Adapted from ref.[12,20,24]

positive patch test usually mimics the exanthema both clinically with erythema and pustules and histologically.[15,17,28] Patch testing should, in the opinion of this author, always be the first in vivo diagnostic aid to be performed. The technique of patch testing drugs in SCARs has been presented extensively in refs.[1,5,28], to which the reader is referred for this subject. When patch tests are negative, intradermal tests or prick tests are the second diagnostic step.

Intradermal tests

The intradermal test (IDT) can be used to identify both immediate and delayed hypersensitivity reactions to drugs. Until recently, these tests were generally considered to be contraindicated in severe cutaneous adverse drug reactions (SCARs: AGEP, drug reaction with eosinophilia and systemic symotoms [DRESS], Stevens-Johnson syndrome/toxic epidermal necrolysis [SJS/TEN]): despite the small doses applied, severe and even fatal reactions have arisen,[20] albeit very infrequently.[29] Currently, however, various authors consider intradermal tests in AGEP to be (potentially) useful and safe when performed by specialists.[25,29,30,31,32,33] Nevertheless, recent guidelines of the European Network in Drug Allergy (ENDA) state that intradermal tests are contraindicated in SCARs.[34] When performed, it is recommended that intradermal tests are done only with drugs available in sterile parenteral commercially manufactured preparations.[34] For the technique and interpretation of IDTs see reference.[34] Nonirritant drug concentrations for intradermal testing can be found in ref.[35] The use of IDT in severe cutaneous adverse drug reactions has been predominantly in the setting of hypersensitivity associated with anti-infective drugs for which the greatest need to know whether they can be safely used exists.[33]

The IDT is generally considered to have increased sensitivity over the patch test and this appears particularly true for antibiotic-associated hypersensitivity reactions[25] and iodinated contrast media.[36] However, similar to the patch test, a negative delayed IDT does not exclude the responsibility of a drug in a cutaneous adverse drug reaction.[31,33,37]

Prick tests

In delayed cutaneous adverse drug reactions, skin prick tests (SPTs) with commercial drugs read after 24 hours have given some positive results in AGEP, DRESS, and maculopapular eruptions.[25,31] However, drug concentration, test protocol, specificity, sensitivity, and safety of prick testing in cutaneous adverse drug reactions (CADRs), including AGEP, are largely unknown.[31,35] Nevertheless, SPTs are often proposed prior to intradermal tests because they may be safer than IDTs.

In addition, skin prick tests can be performed in cases where a sterile injectable form of the offending drug (necessary for intradermal tests) is unavailable.[31,34,35] Nonirritant drug concentrations for prick tests in suspected drug hypersensitivity can be found in ref.[35]

In vitro tests

In vitro tests include the lymphocyte transformation test (LTT) and the enzyme-linked immunosorbent spot (ELISpot) assay. The LTT may be positive in AGEP, especially in cases caused by beta-lactam antibiotics and can help in identifying the culprit drug(s).[38] The test may even have a sensitivity higher than the patch test.[17] The ELISpot assay determines the number of cells that release relevant cytokines and cytotoxic markers after their activation by the culprit drug or their metabolites. IFN-γ ELISpot can be used for evaluating delayed hypersensitivity reactions to beta-lactams. As yet, these two assays are not widely available, because they require specialist equipment and expertise beyond the scope of most routine diagnostic laboratories.[20,38]

Drug-provocation tests

Generally speaking, drug-provocation tests in patients with AGEP and other SCARs are contra-indicated because of the risk of recurrence of the hypersensitivity reaction.[9,29,30,32,37,39] In special circumstances, however, when other diagnostic procedures such as in vivo skin testing and in vitro laboratory tests do not lead to conclusive results, drug-provocation tests may, according to some authors, be performed.[29,31] This applies when there is a compelling need for testing (treatment is necessary and there are no safe and efficacious treatment alternatives) and the benefit of the provocation is far greater than the risk[29,31]; of course, optimal safety measures must be taken and evidence-based recommendations followed. Provocation tests are usually restricted to certain specialist centers in which patients are properly selected and equipment, supplies, and well-trained and experienced personnel are present to manage serious reactions.[37]

2.7 | Treatment

The most important objective is to discontinue the use of the (suspected) causative agent promptly, which typically leads to resolution within days to 2 weeks with characteristic collaret-shaped desquamation of the pustules.[15] Depending on the degree of fever, antipyretics may be advised. Topical steroids are often given and secondary bacterial infections should be treated. In the desquamative phase, skin rehydration measures may be appropriate. Systemic steroids are sometimes prescribed in very extensive eruptions, but there is no evidence that they reduce disease duration. Systemic manifestations should be identified and, whenever needed and possible, appropriately treated.[4]

2.8 | Prognosis

AGEP usually follows a mild course, but high fever, cutaneous superinfection, or multiple organ dysfunction with disseminated intravascular coagulation can complicate the process and lead to severe illness and sometimes life-threatening situations, especially in (elderly) patients of poor general condition.[4] The reported mortality is 1% to 3% or less, especially in the latter patient group.[2,4,9,17] Long-term sequelae (after complete healing) have not been described.[9]

3 | ACUTE LOCALIZED EXANTHEMATOUS PUSTULOSIS (ALEP)

Acute localized exanthematous pustulosis (ALEP) is a localized variant of AGEP.[3,40,41] ALEP is a rare disease: from its first description in 2005 (ie, under this name)[3] up to July 2020, <40 cases have apparently been described in 21 articles (reviewed in ref.[41]). As with AGEP, there is a female preponderance (77%), with a mean age of 38 and age range of 9-78 years. ALEP is most frequently located on the face, followed by the trunk and the arms.[41] The skin reaction with erythema and multiple nonfollicular pustules arises quickly, typically within a few hours to 2-4 days (sometimes longer, up to 10 days) after intake of the drug. It may or may not be accompanied by fever and neutrophilic leukocytosis, but there are no other systemic manifestations.[41]

In >80% of cases, ALEP is caused by systemic drugs, most often beta-lactam antibiotics, especially amoxicillin and amoxicillin-clavulanic acid.[41] Cases have also been linked with topical or systemic exposure to herbal substances[41,42] and to a spider bite.[43] In some patients, no cause/trigger for ALEP can be found (idiopathic).[41] The following diagnostic criteria have been proposed: localized numerous small (1-3 mm) clustered nonfollicular pustules, background erythema, negative microbiology, acute onset (<72 hours) after medication, and resolution with postpustular desquamation within 14 days of discontinuing medication.[44]

Analogous to AGEP, ALEP is thought to be due to drug-specific T cell–mediated immune processes, as shown by positive patch tests and lymphocyte transformation tests[45] in response to culprit drugs. Patch tests have infrequently been performed in ALEP; positive reactions have been observed only to amoxicillin-clavulanic acid,[40] bemiparin,[46] iomeprol,[36,47] metronidazole,[48] and nimesulide.[5]

4 | RESULTS OF LITERATURE REVIEW

The results of the literature review of positive patch tests in AGEP are summarized in Table 3, showing in five columns from left to right the following data: drugs causing AGEP, number of patients with positive patch tests, patch test concentrations and vehicles used, comments/additional information, and references. Details of most case reports can be found in the author's book *Monographs in contact allergy*, *volume 4*: *Systemic drugs*.[5] It should be mentioned that in some studies, no clinical details were provided—only drugs causing AGEP and inducing a positive patch test being tabulated. The data on patch test concentrations, vehicles, and times of reading were in many reports incomplete, not specific, or even completely absent. In some cases, data on patch testing were unavailable to the author. In addition, it was frequently unclear whether the drugs taken by the patient

TABLE 3 Reported cases of acute generalized exanthematous pustulosis (AGEP) with positive patch tests[a,b]

Drug	No. positive patients	Patch test concentration and vehicle[a]	Comments/additional information	Reference no.
Acetaminophen (paracetamol)	1	5% pet.	Also positive patch test to culprit drug amoxicillin (MDH); histology of patch test similar to AGEP	49
	1	5% and 20% in saline and pet.	Patch test and histology similar to AGEP; recurrence after involuntary challenge with the related propacetamol (which is metabolized into paracetamol (acetaminophen)	50
	1	10% pet.	Pediatric patient. PPPT.	51
	1	1% and 10% pet.	Patch tests were negative on two occasions; however, on day (D)7 of the first test session and D6 of the second, a symmetric vesicular eruption appeared on the trunk, arms, and legs	52
Acetaminophen-dextropropoxyphene	2	CP 30% pet.	The two ingredients were not tested separately	27
Acetazolamide	2	CP 30% pet.		53
Acyclovir	1	See right column	The patient was patch tested with acyclovir 10% pet., commercial creams containing acyclovir at 2% or 5%, and pure acyclovir in different vehicles (water, pet., dimethyl sulfoxide, propylene glycol) and concentrations (2%-10%). Positive reactions only with three commercial topical formulations of acyclovir with infiltrated erythema and micropustules; histologic changes similar to AGEP; patch tests with the excipients of the creams were negative	54
	1	1%, 5%, and 10% pet.	Probably previous sensitization by topical acyclovir	55
Amoxicillin	7	Trihydrate 10% pet.		56
	5	Trihydrate 10% pet.	One also had a positive patch test to enoxaparin and another to beclomethasone (both MDH)	27
	3	CP 30% pet. and pure drug 10% pet.		57
	2	10% saline		26
	2	Data unknown	The patients were twins; both later developed acute pustular psoriasis	58
	1	Not specified	Also positive patch test to culprit drug prednisolone (MDH)	59
	1	5% pet.	Also positive patch test to culprit drug acetaminophen (paracetamol) (MDH); histology of patch test similar to AGEP	49
	1	Trihydrate 10% pet.		60
	1	Not specified	Also positive patch test to culprit drug ampicillin; life-threatening involvement of the lungs, heart, liver, and kidneys	61

TABLE 3 (Continued)

Drug	No. positive patients	Patch test concentration and vehicle[a]	Comments/additional information	Reference no.
	1	CP 10% and 30% pet.	Life-threatening hypotension and deteriorated organ function mimicking septic shock; PPPT with AGEP histology	62
	1	Not specified	PPPT	63
	1	Trihydrate 10% pet.	Also reaction to culprit drug floxacillin; patch test again positive after 6.5 years	64
	1	CP 375 mg/0.5 mL PBS		65
	1	1% and 5% pet.	Termed toxic pustuloderma by the authors	66
	1	CP 250 mg/mL		67
	7		See amoxicillin/clavulanic acid, refs.	65,68,69,70,71,72,73
Amoxicillin-clavulanic acid[b]	2	CP 30% or 10% pet. (ns)		27
	1	Crushed tablet solution in water or olive oil	PPPT	74
	1	CP 10% pet.	Massive painful lymphadenopathy; positive patch tests to amoxicillin/clavulanic acid, amoxicillin and ampicillin 10% pet.	68
	1	Amoxicillin 5% pet.	Positive reaction to amoxicillin; cross-reactions to benzylpenicillin and cefalexin	69
	1	CP 185 mg/0.5 mL PBS	Drug-specific T cells were found for amoxicillin, but amoxicillin was not patch tested separately	65
	1	Amoxicillin trihydrate 10% pet.	Cross-reactions to other penicillins	70
	1	Amoxicillin, concentration and vehicle ns		71
	1	CP 10% pet.	Pediatric patient	75
	1	CP 1%, 5%, and 10% pet.		76
	1	Amoxicillin 10% and 1% water		72
	1	Data unknown	The patient had positive patch tests to amoxicillin, clavulanic acid, and enoxaparin (MDH)	73
	1		See clavulanic acid, ref.[77]	
Ampicillin	1	Not specified	Also positive patch test to culprit drug amoxicillin; life-threatening involvement of the lungs, heart, liver, and kidneys	61
Ampicillin-cloxacillin	1	i.v. powder 0.05%, 0.1%, 0.5%, 1%, and 10% water	The two ingredients were not tested separately	78
Ampicillin-sulbactam	1	Not specified	Patch tests were positive to benzylpenicillin and penicillin V; ampicillin/sulbactam was not tested	63
	1	Ampicillin i.v. powder 10% and 30% saline	Pediatric patient	79
Apronalide	1	1% and 10% pet.	Synonym: Allylisopropylacetylurea	80
Bacampicillin	1	10% pet.	PPPT with AGEP histology; also pustular patch test reactions to amoxicillin and sultamicillin tosylate	81

(Continues)

TABLE 3 (Continued)

Drug	No. positive patients	Patch test concentration and vehicle[a]	Comments/additional information	Reference no.
Beclomethasone	1	30% or 10% pet. (ns)	Also positive patch test to culprit drug amoxicillin (MDH)	27
Bendamustine	1	CP 5% and 10% pet.		82
Benznidazole	1	5% DMSO	PPPT with satellite pustules	83
Benzylpenicillin	1		See ampicillin and amoxicillin, ref.[61]; benzylpenicillin was also involved in AGEP, but a patch test with it was apparently not performed or negative; a positive delayed intradermal test proved delayed-type hypersensitivity to benzylpenicillin	
Betamethasone sodium phosphate	1	Dexamethasone eye drops and 1% pet.	The patient had been sensitized from dexamethasone in eye drops and developed AGEP from intramuscular betamethasone sodium phosphate (which could not be patch tested as the patient died)	84
Bleomycin	1	CP 30% pet.		85
Bupropion	1	CP 30% pet.; pure drug 1%, 5%, 10%, and 20% pet.	The patient had been treated with bupropion/naltrexone, which was patch test positive (CP 30% pet.); later, the patient developed classic psoriasis; this may have been AGEP inducing psoriasis from a Koebner phenomenon or generalized pustular psoriasis	86
Carbamazepine	1	1% pet.		26
	1	Data unknown	Later, the patient developed DRESS from phenytoin and valproic acid with positive patch tests (MDH)	87
	1	Data unknown	Patch tests reproduced the skin eruption	88
Carbimazole	1	CP 30% water and pet.	PPPT	89
Cefixime	1	Data unknown		90
Cefotaxime	1	Not specified		91,92
Cefpodoxime	1	Cefotaxime 10% pet.	Cefpodoxime itself was not tested, but positive patch tests to cefotaxime and various penicillins	56
Ceftriaxone	1	10% pet.		27
	1	10% pet.		56
	1	10%, 1%, and 0.1% pet.	Pediatric patient; mild flare on the gluteal region during patch testing	93
	1	Parenteral powder 10% in saline	Pediatric patient; PPPT	94
	1	5% pet.	PPPT	95
Cefuroxime	1	Not specified	Previously, the patient had anaphylaxis from erythromycin; also maculopapular eruptions from valproic acid, gabapentin, mirtazapine, and pregabalin with positive patch tests (MDH)	59

TABLE 3 (Continued)

Drug	No. positive patients	Patch test concentration and vehicle[a]	Comments/additional information	Reference no.
	1	Cefotaxime 10% pet.	Cefuroxime itself was not tested, but positive patch tests to cefotaxime and various penicillins	56
Celecoxib	1	CP 100 mg/0.5 mL PBS		65
	1	CP 5% in pet. and saline		96
	1	1% (vehicle?)		97
	1	Data unknown		98
Cetirizine	1	CP "powdered in pet." and 1 mg/mL solution		99
Chloramphenicol	1	500 mg/mL water	Also positive patch test to culprit drug codeine (MDH); positive intravenous challenge with 1/20 of the therapeutic intravenous dose	100
Ciprofloxacin	1	Not specified	PPPT with AGEP histology; no cross-reaction to norfloxacin	101
	1	Data unknown	Cross-reactions to other (unknown) quinolones; patch tests reproduced the original lesional pattern both clinically and histologically	102
	1	CP 10% or 25% pet. (ns)		103
	1	10% pet.	Cross-reactions to norfloxacin and lomefloxacin	104
Clavulanic acid	1	See right column	AGEP from amoxicillin-clavulanic acid; positive patch test to commercial preparation 30% pet.; amoxicillin was negative; diagnosis of delayed-type hypersensitivity to clavulanic acid made *per exclusionem*; photograph of "positive" patch test not very convincing	77
	1		See amoxicillin-clavulanic acid, ref.[73]	
Clindamycin	2	Not specified	Dutch pharmacovigilance center data	105
	2	10% pet.		106
	2	1% pet.	Not very convincing cases; in one patient PPPT	107
	1	Not specified	AGEP after previous episode of DRESS caused by phenytoin, but negative PT to phenytoin	59
	1	10% pet.		27
	1	10% pet.		108
	1	10% pet.	Also positive patch tests to diltiazem and captopril, but the significance of this finding was not mentioned	109
	1	Data unknown	Apparently the patient had acute kidney injury	110
Cloxacillin	1	CP 30% water and pet.		111
	1	See right column	The patient was not patch tested with cloxacillin, but had positive reactions to benzylpenicillin and penicillin V, tested CP 10% a.i. or CP 30% pet. (ns)	56

(Continues)

TABLE 3 (Continued)

Drug	No. positive patients	Patch test concentration and vehicle[a]	Comments/additional information	Reference no.
Codeine	1	0.5% pet.	Also positive patch test to culprit drug chloramphenicol (MDH)	100
Dexamethasone sodium phosphate	1	Solution for subcutaneous injection	PPPT with AGEP histology	112
Dextropropoxyphene	1	CP 5% and 20% in pet. and water		113
Dicloxacillin	1	10% pet.		104
Diltiazem	2	CP 30% pet. (3% a.i.) and pure drug 10% pet.	One patient developed an angry back reaction associated with maculopapular exanthema involving her face, neck, and armpits; the other had a PPPT; the authors suggested starting patch testing with 1% pet. instead of 10%	114
	1	1% saline		26
	1	Not specified	PPPT	63
	1	10% pet.	Co-reaction to verapamil, another calcium channel blocker	115
	1	1% pet.		116
	1	CP 5% and 20% in pet. and water	Three episodes of AGEP from diltiazem	117
	1	1% water and pure	Patch testing resulted in an erythematous and very pruriginous reaction on the patch tested area, neck and abdomen, that resolved in a few days	118
	1	Not specified	PPPT	71
	1	Not specified		26
	1	1% pet.	Atypical case with flare after 2 weeks; no reactions to other calcium channel blockers (verapamil, nifedipine); eczematous eruption on both forearms during patch testing	119
	1	CP 30% water		120
	2		For other single case reports, **see refs.**[121, 122]	
Enoxaparin	1	30% or 10% pet. (ns)	Also positive patch test to culprit drug amoxicillin (MDH)	27
	1	Data unknown	Also positive patch test to amoxicillin and clavulanic acid (MDH)	73
Eperisone	1	Dilution series 30% to 1% (probably CP)	Positive patch tests to all concentrations; PPPT to 10% and 30% concentrations	123
Eprazinone	1	Pulverized tablet moistened with water	AGEP histology of PT; severe kidney damage	124
Ertapenem	1	CP 10 and 30% water	PPPT; cross-reactions to benzylpenicillin, meropenem, and cefalotin	125
Erythromycin	1	Crushed tablet and i.v. powder in saline	Also positive reaction (PPPT with AGEP histology) to culprit drug spiramycin	126

TABLE 3 (Continued)

Drug	No. positive patients	Patch test concentration and vehicle[a]	Comments/additional information	Reference no.
Etoricoxib	1	CP 1%, 10%, and 30% pet.	Cross-reaction to celecoxib but not to parecoxib	127
Floxacillin (flucloxacillin)	1	CP 10% (a.i.) pet. or water (ns)	Also positive patch test to culprit drug amoxicillin; patch test again positive after 6.5 years	64
	1	CP 10% and 30% water and pet.	Features resembling toxic epidermal necrolysis (TEN) and pronounced systemic symptoms with hemodynamic and respiratory instability	128
Fluconazole	1	Not specified		129
Fluindione	1	CP 30% or 10% pet. (ns)	Also positive patch tests to culprit drugs pristinamycin and an unspecified proton pump inhibitor (MDH)	27
	1	CP 30% pet.		130
	1	CP 30% pet.	Dubious case; patch test was? +; also fever, arthralgia, elevated liver enzymes, and kidney involvement including acute renal failure, hematuria, and proteinuria; possibly DRESS with cutaneous features resembling AGEP	131
Gadobutrol	1	CP 1.0 mmoL/mL	PPPT	132
Hydroquinidine (dihydroquinidine)	1	Crushed tablet in saline	PPPT with AGEP histology	126
Hydroxychloroquine	1	10% in DMSO	PPPT with AGEP histology	133
	1	Not specified		134
	1	CP 20% and 50% pet.	Pediatric patient	135
	1	CP 30% pet.		136
Hydroxyzine	1	10% pet.	AGEP histology of patch test; patient also presented in refs.138, 139	137
	1	Pure drug 2.5% pet.	PPPT; no (pseudo)cross-reactions to cetirizine or levocetirizine; flare-up of previously involved areas during patch testing	140
	1	CP 30% pet. and pure drug 10% pet.		57
	1	No details provided	The drug used was hydroxyzine pamoate	141
	1	CP 10% pet.	The drug used was hydroxyzine pamoate	142
Ibuprofen	1	Combination tablet and ibuprofen 10% pet.	PPPT	143
Iobitridol	1	CP undiluted		144
Iodixanol	2	CP "as is" or between 10% and 30% pet. (ns)		36
	2	CP "as is"		144
	1	30% or 10% pet. (ns)		27
	1	CP "as is"		145
Iohexol	1	CP "as is" or between 10% and 30% pet. (ns)		36
Iomeprol	6			36

(Continues)

TABLE 3 (Continued)

Drug	No. positive patients	Patch test concentration and vehicle[a]	Comments/additional information	Reference no.
		CP "as is" or between 10% and 30% pet. (ns)	Six positives in a group of eight patch tested with iomeprol, but the patients had been highly selected	
	1	CP "as is"		144
	1	CP "as is" (probably)	Cross-reactions to seven other iodinated contrast media	146
Iopamidol	1	Not specified		147
Iopromide	1	CP undiluted	Cross-reactions to three other iodinated contrast media	148
	1	CP "as is" or between 10% and 30% pet. (ns)		36
Ioversol	1	30% or 10% pet. (ns)		27
	1	CP 30% water	Three episodes, the first two ascribed to antibiotics	149
	1	CP "as" is or between 10% and 30% pet. (ns)		36
Isepamicin	1	10% pet.		150
Isoniazid	1	1% pet.	PPPT; flare-up after oral provocation	151
Labetalol	1	5% water and pet.	PPPT; with patch test no cross-reaction to atenolol 10% water and pet., but an oral provocation with atenolol resulted in generalized itching and micro-papules on the back and arms, starting after 1 hour	152
Lansoprazole	1	CP omeprazole 5% and 20% pet.	Apparently, lansoprazole itself was not available for patch testing	153
Lincomycin	1	1% and 20% pet. (CP?)		154
Metamizole	1	CP 10% and 20% water		155
Methoxsalen	1	Data unknown		156
Methylprednisolone sodium hemisuccinate (or acetate)	1	See right column	There were positive patch tests to prednisolone, tixocortol pivalate, and hydrocortisone; the culprit drug itself was apparently not patch tested, but would almost certainly have been positive	157
Metronidazole	1	1% pet.	In the first report (ref.[158] also presented in abstract form in refs.[159, 160]). The patient had a positive patch test to metronidazole 0.75% cream, but metronidazole itself or the cream base were not available; 6 years later, a patch test was positive to metronidazole 1% pet.[116]	116,158
Mexiletine	1	CP 10% and 20% pet.		161
Miconazole	1	CP 30% pet.		162,163
Minocycline	1	10%, vehicle ns		164
Morphine	1	CP 10 mg/mL and pure drug 1% water	In another patient, AGEP may have been caused by *topically* applied morphine ref. 166	165
Nifuroxazide	1	CP 10% water and pet.	PPPT with AGEP histology	167
Nylidrin (buphenine)	1	Data unknown	PPPT	168

TABLE 3 (Continued)

Drug	No. positive patients	Patch test concentration and vehicle[a]	Comments/additional information	Reference no.
Nystatin	3	CP "as is" (n = 3); pure drug 10% pet.		169
	1	2% pet.	PPPT with AGEP histology	170
	1	CP and pure drug, details unknown		171
	1	CP 10% and 30% in pet. and water	Only scratch patch tests were positive	172
Oxacillin	1	CP 30% pet.	PPPT	173
Phenobarbital	1	1% pet.		26
Prednisolone	1	See right column	The patient had been treated with topical prednisolone acetate cream and with systemic prednisolone and prednisolone tetrahydrophthalate; patch tests were positive to prednisone 100 mg/mL PBS but negative to prednisolone and hydrocortisone; however, LTTs were positive to prednisolone and hydrocortisone; despite the negative patch test reaction to prednisolone (which may have been false negative, or late readings were not performed), this was obviously the cause of AGEP, to which topical prednisolone acetate, oral prednisolone, and oral prednisolone tetrahydrophthalate may all have contributed.	174
	1	1% pet.	In addition, positive patch tests to prednisone, hydrocortisone, tixocortol pivalate, and budesonide	174
	1	CP 10% pet.	Patch test with excipients of prednisolone tablets was negative	175
	1	Not specified	Also positive patch test to culprit drug amoxicillin (MDH)	59
	1	Not specified	Also positive patch test to tixocortol pivalate	176
Prednisolone sodium succinate	1	Prednisolone 0.25% (vehicle?)	The authors consistently spoke of "prednisolone," but the drug had been given intravenously and therefore was likely prednisolone sodium succinate; PPPT; the authors had presented the same patient 1 year earlier in another journal (ref. 178); here it was stated that patch tests were positive to prednisolone 1% pet., with erythema and infiltration after 24 hours and additional pustules after 48 or 72 hours with cross-reactions to methylprednisolone (1.6% water) and prednicarbate 2.5% ointment base, histologically mimicking the original disease	177
Prednisolone sodium tetrahydrophthalate	1		See prednisolone, ref.[174]	
Prednisone	2	30% or 10% pet. (ns)		27

(Continues)

TABLE 3 (Continued)

Drug	No. positive patients	Patch test concentration and vehicle[a]	Comments/additional information	Reference no.
Pristinamycin	11	10% pet.	Eleven positives among 21 patients with AGEP	108
	8	CP 30% or 10% pet. (ns)	In one case, also positive patch tests to culprit drugs fluindione and a proton pump inhibitor (ns) (MDH); in one patient, the patch test induced a flare-up of AGEP requiring systemic corticosteroids	27
	3	CP 20% water and pet.	Some may have been sensitized previously to the topical application of the related antibiotic virginiamycin (cross-reaction possible)	179
	2	CP 30% pet.		57
	1	Not specified		180
Propacetamol	1	Paracetamol 5% and 20% in saline and pet.	One year before, the patient had an episode of AGEP from acetaminophen (paracetamol) and had positive patch tests; he was now given intravenous propacetamol, which is metabolized into paracetamol, and had a second AGEP episode	50
Propicillin	1	CP 20% pet.	The patient was diagnosed with AGEP, but this can be doubted as he had *painful follicular* pustules and in the histology, subcorneal pustules were missing	181
Pseudoephedrine	1	1% pet.		27
	1	CP and pseudoephedrine, unspecified	The commercial preparation contained codeine, chlorpheniramine, and pseudoephedrine	182
	1	CP 2.5% and 5% pet.; pure drug 1% pet.		183
	1	Combination preparation pure and CP pseudoephedrine 20% and 50% pet.	The combination preparation contained paracetamol (acetaminophen), chlorpheniramine, and pseudoephedrine	184
	1	10% pet.	AGEP had been caused by the combination of paracetamol and pseudoephedrine; the patch test with paracetamol was negative	185
	1	See right column	The patient had taken a combination tablet of fexofenadine and pseudoephedrine; there was a positive reaction to the tablet 30% pet. but negative to fexofenadine; pseudoephedrine was not tested and diagnosed as culprit drug *per exclusionem*	186
Ranitidine	1	Tablet "dispersed in petrolatum"	PPPT	187
Ritodrine	1	1%, 0.1%, 0.05%, and 0.01% water		188
Spiramycin	1	5% pet.		26

TABLE 3 (Continued)

Drug	No. positive patients	Patch test concentration and vehicle[a]	Comments/additional information	Reference no.
	1	CP 30% pet.		108
	1	Crushed tablet and i.v. powder in saline	Also positive reaction (PPPT with AGEP histology) to culprit drug erythromycin	126
	1	CP 10% pet. and saline		189
	1	Not specified		180
	1	CP 30% pet. and pure drug 10% pet.		57
Terbinafine	1	CP 30% pet.	PPPT	190
	1	Not specified	PPPT	191
Tetrazepam	1	30% or 10% pet. (ns)		27
	1	1% and 5% pet. and water	The patch test became positive on D10 only	192
Ticlopidine	1	5% and 10% water and pet. (CP or pure drug?)	PPPT	193
Vancomycin	1	Not specified		194
	1	CP 30% pet.		195
Varenicline	1	30% or 10% pet. (ns)		27
	1	CP 1%, 5%, 10%, and 30% pet. and water	Positive patch tests to 5%, 10%, and 30% pet.; all tests in water were negative	196
Virginiamycin	1	0.5% pet.		26

Abbreviations: a.i., active ingredients; CP, commercial preparation; DMSO, dimethyl sulfoxide; MDH, multiple drug hypersensitivity; ns, not specified; PBS, phosphate-buffered saline; Pos., positive; PPPT, ustular positive patch test; PT, atch test.
[a]It was often unclear whether the drugs used by the patient or the pure drug materials were patch tested.
[b]Clavulanic acid itself was patch tested in one report only.[73]

(indicated in column 3 with CP [Commercial Preparation]) had been used for patch testing or that pure drug material had been tested. Because of this frequent lack of specific data, the author cannot guarantee that all information provided in Table 3 is fully accurate.

4.1 | Drugs causing AGEP and showing positive patch tests

In this literature review, the author has found 93 drugs that have together caused 259 positive patch tests in 248 patients with AGEP. The number of reactions is 11 higher than the number of patients, as 9 individuals had reactions to two culprit drugs and 1 reacted positively to three. The drugs most frequently causing positive patch tests in patients with AGEP are shown in Table 4. Amoxicillin heads the list with 36 reactions (of which 7 were in patients with AGEP from amoxicillin/clavulanic acid), followed by pristinamycin (n = 25, 13.9%), diltiazem (n = 14, 9.7%), amoxicillin-clavulanic acid (n = 13, 5.4%), clindamycin (n = 11, 4.2%), and iomeprol (n = 8, 3.1%). Of the 13 patients who had developed AGEP from amoxicillin-clavulanic acid, 6 were allergic to amoxicillin, 1 to clavulanic acid + amoxicillin, 1 to clavulanic acid (established *per exclusionem*, amoxicillin was negative), and 5 reacted only to the combination product—the ingredients were not tested separately. Thirteen drugs caused positive patch tests in two cases and 59 (63%) in only one.

The classes of drugs causing the highest number of reactions are beta-lactam antibiotics (n = 67 [25.9%], of which 36 were to amoxicillin), other antibiotics (n = 54 [20.8%], of which 25 to pristinamycin, 11 to clindamycin, and 6 to spiramycin), iodinated contrast media (n = 19 [7.3%]), and corticosteroids (n = 14 [5.4%]).

4.2 | Sensitivity of patch testing in patients with AGEP

There are few data on the sensitivity of patch testing in AGEP (Table 5). Percentages of positive reactions have ranged from 18% to 75%, but the studies are incomparable and sometimes highly selected. In two more French studies (all but one [Portugal, ref.[104]] are from France), 50% of positive patch tests to drugs causing AGEP were positive, but more details are not known.[197,198]

4.3 | Optimal patch-test concentrations and vehicles

As shown in Table 3, a large range of concentrations have been used for drug patch tests in patients with AGEP. In many cases, the commercial preparations taken by the patients, often tablets, have been pulverized

and the powder used for patch testing in concentrations ranging from 10% to 30%, mostly in petrolatum, and sometimes (also) in water. Pure drugs were tested in a minority of cases, probably due to difficulties to obtain these. There are no published studies in which all drugs suspected of causing AGEP have been patch tested with various test concentrations and vehicles in a considerable number of patients and with the results fully specified. From the studies presented thus far, no evidence for the optimal patch test concentration and vehicle for any drug has emerged.

TABLE 4 Drugs most frequently causing positive patch tests in patients with AGEP[a]

Drug	No. positive patch tests	%
Amoxicillin	36	13.9
Pristinamycin	25	9.7
Diltiazem	14	5.4
Amoxicillin-clavulanic acid	13	5.0
Clindamycin	11	4.2
Iomeprol	8	3.1
Iodixanol	6	2.3
Nystatin	6	2.3
Pseudoephedrine	6	2.3
Spiramycin	6	2.3
Ceftriaxone	5	1.9
Hydroxyzine	5	1.9
Prednisolone	5	1.9
Acetaminophen (paracetamol)	4	1.5
Celecoxib	4	1.5
Ciprofloxacin	4	1.5
Hydroxychloroquine	4	1.5
Ampicillin	3	1.2
Carbamazepine	3	1.2
Fluindione	3	1.2
Ioversol	3	1.2

[a]Only drugs that have caused at least 3 positive patch test reactions in patients with AGEP are included; Nr. PPT Number of positive patch tests.

4.4 | Safety of patch testing in AGEP

In 26 patients with AGEP who had one or more positive patch tests, only one relapse of AGEP was observed that required systemic corticosteroids, following a positive patch test with pristinamycin.[27] A few more cases of exacerbations of the AGEP drug eruption or another skin rash during or following patch testing have been found, but systemic symptoms (eg, fever, leukocytosis, elevated CRP, elevated liver enzymes) have not been reported (Table 6). Three reactions were caused by diltiazem, in (at least) four cases the suspected drug was tested in two or three concentrations,[52,93,114,118] and in another, there were also one or more additional positive patch test reactions.[102]

5 | DISCUSSION

In the interpretation of the results presented in Section 4 and the discussion in Section 5, it should be realized that it is unknown which proportion of patients with diagnosed AGEP has been patch tested (neither percentage nor culprit drugs); that selection may have influenced the available data (eg, investigating and presenting only patients treated with certain antibiotics or iodinated contrast media); that clinical data were sometimes and patch data frequently incomplete, unclear, or even absent; that patch tests have not infrequently been read after 24 or 48 hours only (which can lead to both false-negative and false-positive results); and that geographically, most patch testing has been practiced in a limited number of countries, which may influence results (eg, the large number of positive patch test reactions to pristinamycin and spiramycin, drugs that are widely used in France).

5.1 | Drugs causing AGEP and showing positive patch tests

According to this literature review, 93 drugs that have caused AGEP also induced a positive patch test reaction, with a total of 259 positive tests. The classes of drugs causing the highest number of reactions

TABLE 5 Sensitivity of patch testing in AGEP

Drugs	No. patients tested[a]	Nr. Positive	(%)	Comments	Ref.
Groups of patients					
Drugs not specified	14	7	50	The drugs reacting positively were mentioned, but the negative drugs not specified	26
	45	26	58	Many reactions to pristinamycin and amoxicillin	27
Classes of drugs					
Antibiotics	11	2	18	Unknown which antibiotics had been tested negative	104
Individual drugs					
Iomeprol	8	6	75	The patients had been selected on the basis of a positive skin or challenge test	36
Pristinamycin	21	11	52		108

[a]Minimally five patients patch tested with individual drugs.

TABLE 6 Exacerbations of AGEP symptoms after patch testing

Drug	Patch test concentration and vehicle	Symptoms and comments	Ref.
Acetaminophen	1% and 10% pet.	On D7 of a first and D6 of a second patch test session, a symmetric versicular eruption appeared on the trunk, arms and legs; the patch tests themselves were negative	52
Carbamazepine	Data unknown	Patch tests reproduced the skin eruption	88
Ceftriaxone	10, 1 and 0.1% pet.	Mild flare reaction consisting of papules and vesicles with erythema on the gluteal region during patch testing	93
Ciprofloxacin	Data unknown	Patch tests reproduced the original lesional pattern both clinically and histologically; there were also positive patch tests to other quinolones	102
Diltiazem	1% water and pure	Patch testing resulted in an erythematous and very pruriginous reaction on the patch tested area, neck, and abdomen that resolved in a few days	118
Diltiazem	1% pet.	Eczematous eruption on both forearms during patch testing; atypical AGEP case	49
Diltiazem	CP 30% pet. (3% a.i.) and pure drug 10% pet.	Patch testing induced an angry back reaction associated with maculopapular exanthema involving the face, neck, and armpits, but there were no systemic reactions; the authors suggested to start patch testing with 1% pet. instead of 10%	114
Hydroxyzine	Pure drug 2.5%	Flare-up of previously involved areas during patch testing	140

are beta-lactam antibiotics, other antibiotics, iodinated contrast media, and corticosteroids, together accounting for nearly 60% of all reactions (Section 4.1). The highest numbers of reactions were caused by amoxicillin, pristinamycin, diltiazem, amoxicillin-clavulanic acid, clindamycin, and iomeprol. The "Top-10" drugs together caused over 50% of all reactions (Table 4). Only 21 drugs caused AGEP with established positive patch tests in at least three cases and, of these, only 5 more than 10 reactions. One of these was pristinamycin (25 reactions), which may bias the data, as this drug may be used mainly in France, and the great majority of patch test studies in SCARS with case series have been performed in that country. Conversely, 59 drugs (63% of the total) each caused one AGEP reaction with a positive patch test only.

5.2 | Sensitivity of patch testing in patients with AGEP

There are very few data available on the sensitivity of patch testing in patients with AGEP (Section 4.2, Table 5). Large-scale studies in which all drugs tested were specified are not available. Indeed, the rarity of AGEP makes collecting massive data very difficult, even in multicenter studies such as performed by the Toxidermies group of the French Society of Dermatology.[27] In their study, 26 of 45 patients with AGEP (58%) had positive reactions, which supports patch testing as a useful diagnostic aid in AGEP. It should be mentioned that, in this study, eight reactions were caused by pristinamycin, which often reacts positively.[108] This particular antibiotic (as is also the case with the culprit drug fluindione and spiramycin) may be little used outside France. Patch testing in patients with AGEP with the drugs that have most frequently caused positive patch tests—such as amoxicillin, pristinamycin, diltiazem, amoxicillin-clavulanic acid, clindamycin, iomeprol, iodixanol, nystatin, pseudoephedrine, and others—may be rewarding, but how often patch tests to individual drugs in patients with AGEP are positive is, with the exception of pristinamycin, as yet unknown.

5.3 | Optimal patch-test concentrations and vehicles

The literature review does not give any indication of the optimal or preferred patch-test concentrations and vehicles for individual drugs. For the technique of patch testing drugs in SCARs the reader is referred to refs.[1, 5, 28]

5.4 | Safety of patch testing in AGEP

Patch testing in AGEP appears to be safe. Only a few cases of exacerbations of the AGEP eruption or another skin rash during or following patch testing have been found in literature, all without systemic manifestations (Section 4.4, Table 6). Risk factors may be testing the drug in two or three patches and additional positive patch tests. Three of the nine reported cases have been caused by diltiazem. Patch testing this calcium channel blocker first with 1% pet. instead of the usual

and commercially available 10% pet. has been suggested,[114] and may have merit. Nevertheless, in one case of AGEP, albeit an atypical one, testing diltiazem in this low concentration still resulted in a mild eczematous reaction on the forearms.[119]

CONFLICTS OF INTEREST

Anton de Groot is the author of *Monographs in contact allergy*, *Volume 4 - Systemic drugs*, Boca Raton, Fl, USA: CRC Press Taylor and Francis Group, 2022 (ISBN 9780367436490), to which book is referred repeatedly in this article.

DATA AVAILABILITY STATEMENT

Research data are not shared

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