

Patch Testing for Evaluating Drug Reactions Due to Systemic Antibiotics

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Several studies have evaluated patch testing for the diagnosis of drug eruptions, but widespread acceptance of this procedure is lacking in North America. The objective of this review is to address patch testing for the evaluation of exanthematous drug eruptions due to systemic antibiotics, using a MEDLINE database search for articles in English on patch testing for systemic drug eruptions caused by antibiotics

DERMATOLOGISTS are frequently consulted for cutaneous drug eruptions, especially in hospitalized patients. Approximately 2 to 3%^{1,2} of inpatients experience a cutaneous drug eruption, and 46 to 95%^{3,4} of these cutaneous reactions are exanthems. Physicians often face difficult diagnostic challenges when patients are taking multiple drugs and have confounding medical problems that can also cause cutaneous eruptions. Physical examination, a detailed clinical history, and skin biopsy are the main instruments of investigation. Unfortunately, there is no reliable diagnostic test that confirms a specific drug as the culprit other than an oral rechallenge, which is laborious and potentially life threatening and so is rarely performed. The pathophysiology of exanthematous drug eruptions is not fully understood but they are commonly attributed to delayed-type hypersensitivity. Thus, patch testing with oral medications has been investigated as a possible diagnostic tool. This practice is more common in Europe than in the United States. The purpose of this review is to summarize the existing literature on patch testing with systemic medications. We were specifically interested in evaluating the efficacy, relevance, and safety of patch testing with systemic antibiotics for the diagnosis of cutaneous drug reactions.

Methods

In this systematic review, we used *Ovid* software (Ovid Technologies, Inc., New York, NY) to search MEDLINE

articles published from 1966 to August 2005 in English, using the keywords "patch test," "skin test," "drug hypersensitivity," "drug eruption," and "antibiotic." We searched for publications that dealt with any systemic drug eruption evaluated by patch testing. The majority of studies evaluating patch testing with systemic medications originated in Europe except for the study by Calkin and Maibach,⁵ who were among the first to review the literature on patch testing with systemic drugs. Our review specifically focused on patients with a history of a drug exanthem due to systemic antibacterial agents. We found the descriptions "exanthem" and "maculopapular" to be synonymous. In many cases, data were not reported separately for either drug exanthems or antibiotics. In these situations, we contacted the author whenever possible and, if data were unavailable, listed categorical data. Whereas a number of studies included other skin tests (such as skin-prick, intradermal, and photopatch tests), we focused specifically on patch testing and oral challenge tests. For assessments of validity and predictive value, oral challenge tests were defined as the "gold standard" for the diagnosis of systemic allergy to medications. Finally, we performed statistical analyses, if not already calculated in the original manuscripts, using Pearson chi-square tests with 1 degree of freedom and (in certain cases) Fisher exact tests, with SAS software (*Statistical Analysis System*, SAS Institute Inc., Cary, NC). These are identified as "calculated" in the text.

Mechanisms of Allergic Reactions to Systemic Medications

Allergic reactions are categorized in four groups by the Gell and Coombs classification.⁶ Type I reactions are immediate hypersensitivities, such as urticaria and ana-

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phylaxis, which are caused by the release of histamine and other factors from mast cells and basophils following immunoglobulin E (IgE) cross-linking. Type II reactions are cytotoxic reactions that result from antibody-activated complement system and cell destruction. Type III reactions are caused by the deposition of circulating antigen-antibody complexes. Finally, Type IV reactions are cell-mediated delayed hypersensitivities that result from sensitized T lymphocytes. Unfortunately, many cutaneous drug eruptions are not easily classified into these categories, nor are diagnostic tests available for distinguishing each of these allergic etiologies.

There are three proposed mechanisms explaining how T cells become sensitized to antigens (Fig 1).^{7,8} A drug can act as an antigen either by (1) undergoing metabolism into a reactive compound or (2) binding directly to other molecules as a chemically reactive hapten without intracellular modification; alternatively, a drug can form a labile noncovalent interaction to a major histocompatibility complex peptide and be presented directly to T cells. In theory, some antibiotics may react more readily on patch testing, based on how the drug is presented as an antigen to T lymphocytes.

Based on recent immunohistologic studies and experimental data on drug-specific T-cell lines and clones from patients with drug allergies, type IV allergic reactions can be further classified into four groups, depending on the type of T lymphocyte-mediated immune response and effector cells, including T helper 1 (Th1)-induced monocytes, T helper 2 (Th2)-induced eosinophils, activated cytotoxic cells, or interleukin-8-stimulated neutrophils.⁹ Drug-induced exanthems are thought to be manifestations of type IVc hypersensitivities. In these allergic reactions, drug-specific CD4⁺ T cells release cytotoxic granule proteins such as perforins and granzyme B at the dermoepidermal junction zone, causing vacuolar alteration and keratinocyte cell death (Fig 2).

Patch-Testing Methodology for Systemic Medications

Patch-testing guidelines based on expert opinion for the evaluation of systemic drug eruptions were published by Barbaud and colleagues in 2001.¹⁰ These authors recommended performing patch tests 6 weeks to 6 months after the resolution of the cutaneous drug eruption. (Romano

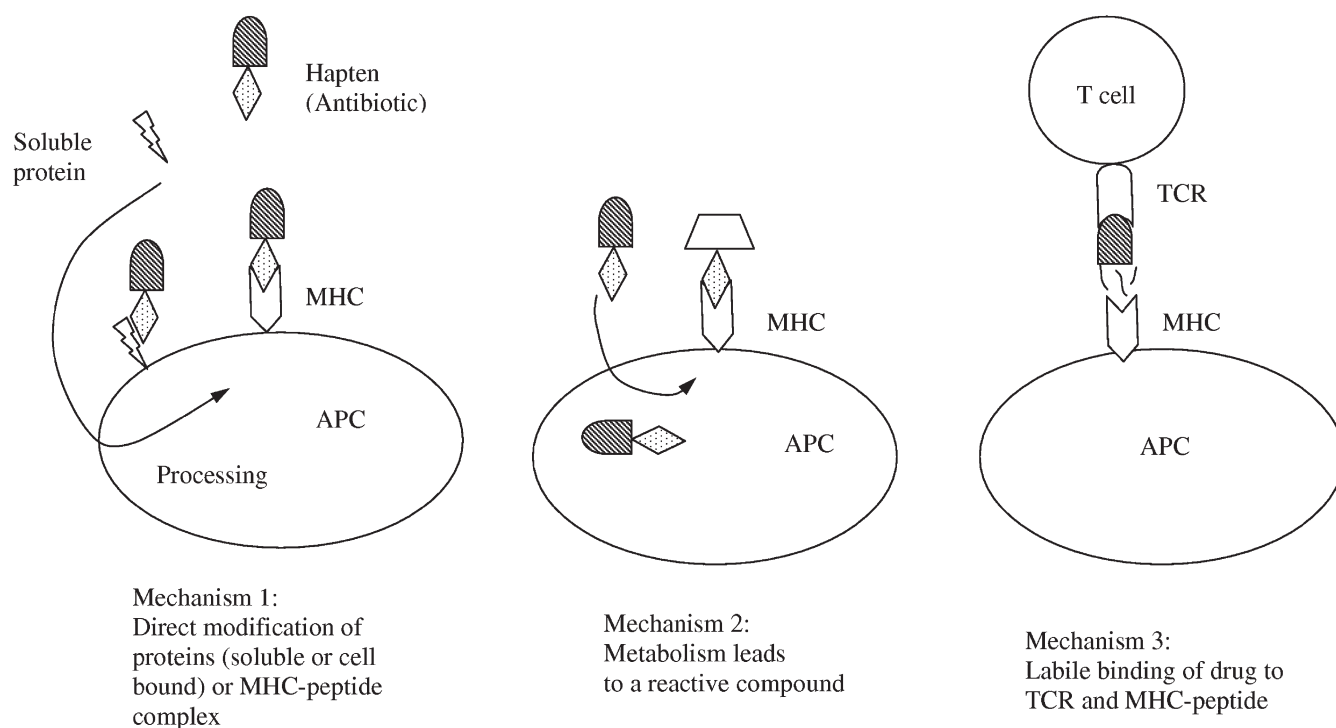


Figure 1. Mechanisms of drug presentation to T cells. First, hapten-like drugs can bind to soluble or cell-bound molecules; subsequently, these complexes can bind to the major histocompatibility complex (MHC) on antigen-presenting cells (APCs). Second, drugs can undergo metabolism to become reactive haptens. Third, a chemically inert drug can bind directly to the T-cell receptor (TCR) in a noncovalent association with the MHC molecule. (Adapted from Pichler WJ.⁸)

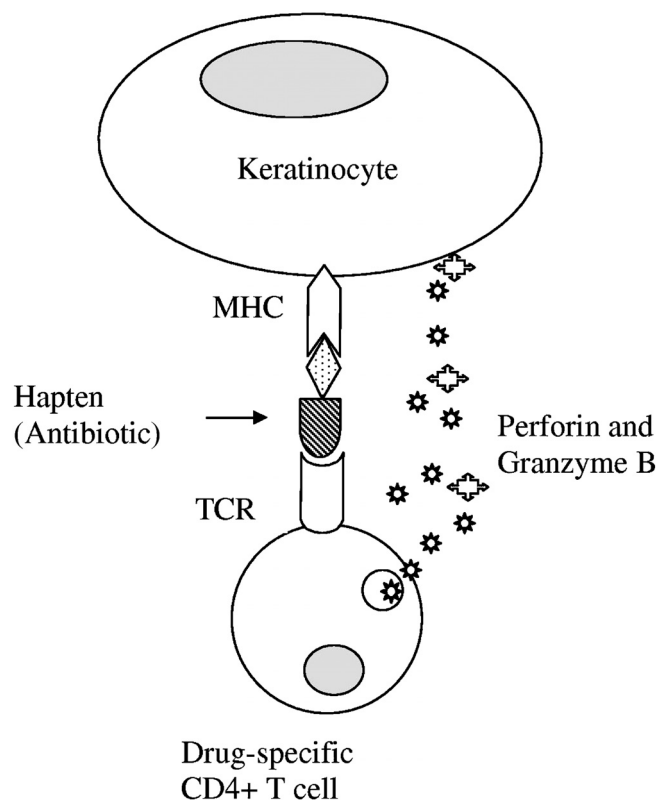


Figure 2. CD4⁺-mediated cytotoxicity in drug exanthems. Sensitized CD4⁺ T cells recognize an antigen, interact with the class II major histocompatibility complex (MHC II) on keratinocytes, and release perforins and granzyme B, causing keratinocyte death. (Adapted from Pichler WJ.⁸) TCR = T-cell receptor.

and colleagues, however, reported that positive patch test reactions lasted over 2 years in 20 patients.¹¹) As in standard patch testing, it is ideal to perform patch testing at least 1 month after systemic immunosuppressive therapy, if possible. The tests should be done on the upper back with standard chambers, such as Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) or IQ Chambers (Chemotechnique Diagnostics, Vellinge, Sweden). The patch tests are read at 20 minutes, on day (D)2 and D4 using standard criteria.¹² If the patch tests are negative on D4, then a reading is recommended on D7. If patch testing is negative, skin prick tests followed by intradermal tests with delayed readings are recommended.

Because systemic drug antigens are generally not commercially available, they must be prepared. If pills are coated, the coating should be removed. The gel jacket of a capsule should be moistened with water and tested “as is.” The interior portion of pills and capsules should be finely ground and then tested at a 30% concentration in two vehicles, white petrolatum and water. Liquid medica-

tions are tested both “as is” and diluted 30% in water. Pure drug from the manufacturer can also be obtained and diluted to 10% in petrolatum, water, or alcohol. For drugs known to reinduce a cutaneous drug eruption (such as acyclovir, carbamazepine, or pseudoephedrine), lower concentrations (ie, 1%) are recommended.¹³ Whenever possible, preservatives and colorings in the medication should also be tested at standard concentrations. Reported patch-test concentrations for systemic antibiotics are listed in Table 1.

Experts have suggested including at least 20 human controls when testing with nonstandardized antigens. The ideal negative control is a patient with a recent history (6 weeks to 6 months) of a cutaneous drug eruption whose cause has been identified. For example, if the control patient has a history of a cutaneous adverse drug reaction after ingesting acetaminophen and clindamycin and this reaction is confirmed either by skin tests or repeat exposure for acetaminophen only, then the patient can serve as a negative control for clindamycin. Because such controls are difficult to identify, healthy volunteers (with or without previous exposure to the drug culprit) can also be used. Finally, dermatologists who are familiar with patch testing and diluting medications should perform these procedures.

Frequency of Positive Patch-Test Reactions

The frequency of positive patch-test reactions in patients with a history of a drug exanthem from any medication is approximately 10 to 11%.^{14,15} Patients with a history of a cutaneous drug exanthem specifically from antibiotics react more frequently (10–46%) when patch-tested (Table 2). Aminopenicillins, cephalosporins, pristinamycin, and clindamycin have higher rates of positive reactions when compared to macrolides, tetracyclines, and quinolones. Investigators who patch-test only patients with a high imputability for a single drug may report a higher frequency of positive reactions (31–100%).

Studies Reporting on Patch Testing with Specific Drugs

Multiple Antibiotics

Many studies have evaluated patch testing with multiple antibiotics. In 2005, Lammintausta and Kortekangas-Savolainen¹⁴ reported on the usefulness of patch tests in

Table 1. Test Vehicles and Concentrations for Selected Antibiotics Used in Patch Testing

<i>Antibiotic</i>	<i>Vehicle</i>	<i>Test concentration</i>	<i>Antibiotic</i>	<i>Vehicle</i>	<i>Test concentration</i>
Aminoglycosides			Fluoroquinolones		
Gentamicin	pet.	20 ⁵³ –30% ¹⁴		pet.	20–30% ¹⁴
	aq.	20 ⁵³ –30% ¹⁴		aq.	20–30% ¹⁴
Antituberculars			Ciprofloxacin	pet.	10–20% ¹⁸
Ethambutol	pet.	1%, ⁵³ 30%, ⁵⁴ 50% ⁵⁵	Levofloxacin	pet.	20% ¹⁸
	aq.	1%, ⁵³ 30% ⁵⁴	Lomefloxacin	pet.	10 ⁵³ –20% ¹⁸
Isoniazid	pet.	20–30%, ¹⁴ 50% ⁵⁵	Norfloxacin	pet.	10%, ⁵⁸ 20 ¹⁸
	aq.	1%, ⁵³ 20–30% ¹⁴			
Rifampin	pet.	As is, ⁵³ 30%, ⁵⁴ 50% ⁵⁵	Sparfloxacin	pet.	20% ¹⁸
	aq.	30% ⁵⁴			
β-lactams			Macrolides		
<i>Aminopenicillins</i>			Azithromycin	pet.	20–30% ¹⁴
Amoxicillin	pet.	As is, ⁵³ 5%, ^{11,21} 20–30% ¹⁴		aq.	20–30% ¹⁴
	aq.	5%, ⁵⁶ 20–30% ¹⁴	Erythromycin	pet.	1%, ⁵³ 10%, ⁵³ 20–30% ¹⁴
				aq.	20–30% ¹⁴
Amoxicillin/clavulanate	pet.	20% ²⁸	Josamycin	pet.	30% ¹⁷
Potassium clavulanate	pet.	10% ⁵⁷		aq.	30% ¹⁷
Ampicillin	pet.	5% ^{11,21}	Roxithromycin	pet.	20–30% ¹⁴
	aq.	5% ⁵⁶		aq.	20–30% ¹⁴
<i>Carbapenem</i>			Spiramycin	pet.	1–5%, ⁵³ 10% ⁵³
Meropenem	pet.	20–30% ¹⁴			
	aq.	20–30% ¹⁴			
<i>Monobactam</i>			Streptogramins		
Aztreonam	pet.	20% ^{20,28}	Dalfopristin/quinupristin	pet.	30% ²²
<i>Penicillins</i>			Pristinamycin	pet.	10%, ²² 20%, ²³ 30% ^{17,22}
Penicillin G	aq.	As is ⁵³		aq.	10%, ²² 20%, ²³ 30% ^{17,22}
Phenoxyethyl penicillin	pet.	20–30% ¹⁴	Virginiamycin	pet.	5% ⁵⁹
	aq.	20–30% ¹⁴			Commercial ointment ²²
Benzylpenicillin	pet.	20–30% ¹⁴			
	aq.	20–30% ¹⁴			
Cloxacillin	pet.	20–30% ¹⁴	Sulfonamides		
	aq.	20–30% ¹⁴	Sulfamethoxazole	pet.	10%, ⁵³ 20–30% ¹⁴
Piperacillin	pet.	20% ¹⁸		aq.	20–30% ¹⁴
			Trimethoprim	pet.	10%, 20–30% ¹⁴
				aq.	20–30% ¹⁴
<i>Cephalosporins</i>			Tetracyclines		
Cefaclor	aq.	1–5% ⁵³	Doxycycline	pet.	As is, ⁵³ 20–30% ¹⁴
	pet.	20–30% ¹⁴		aq.	20–30% ¹⁴
	aq.	20–30% ¹⁴	Tetracycline	pet.	20–30% ¹⁴
Cefadroxil	pet.	20–30% ¹⁴		aq.	20–30% ¹⁴
	aq.	20–30% ¹⁴			
Cephalexin	pet.	20–30% ¹⁴			
	aq.	20–30% ¹⁴			
Cefazolin	pet.	20% ¹⁸	Others		
	aq.	1–5% ⁵³	Clindamycin	pet.	1%, ⁵³ 10–30% ^{14,24}
Cefpirome	pet.	20% ¹⁸		aq.	1%, ⁵³ 10–30% ^{14,24}
Ceftazidime	pet.	20% ^{18,28}	Chloramphenicol	pet.	5% ⁵³
Ceftizoxime	pet.	20% ¹⁸		aq.	500mg/mL ⁶⁰
Ceftriaxone	pet.	20–30% ¹⁴	Metronidazole	pet.	2%, 20–30% ¹⁴
	aq.	20–30% ¹⁴		aq.	20–30% ¹⁴
Cefuroxime	pet.	10%, ⁵³ 20–30% ¹⁴	Nitrofurantoin	pet.	5%, 20–30% ¹⁴
	aq.	20–30% ¹⁴		aq.	20–30% ¹⁴
			Vancomycin	aq.	0.005% ⁶¹

alc. = alcohol; aq. = water; pet. = petrolatum.

Table 2. Summary of Reported Studies on Patch Testing with Systemic Antibiotics

Study	Single Drug Imputability? (Drug)	Study Design				No. +PT in Pts with EX and Abx	No. of Controls	Mean Time Interval between Drug Eruption and PT	Test Concentration and Vehicle for Abx
		No. Pts Tested with EX	No. Pts Tested for Abx	No. +PT in all Pts	No. +PT in Pts with EX				
Patriarca et al ²⁵ (1999)	Yes (β-lactams)*	20/30 (67%)	30/30 (100%)	30/30 (100%)	20/20 (100%)	20/20 (100%)	20	6 yr (10 d – 25 yr)	50 mg/mL (pet)
Lisi et al ²⁰ (1997)	Yes (β-lactams)	32/101 (32%)	101/101 (100%)	21/101 (21%)	10/32 (31%)	10/32 (31%)	NR	NR	20–25% (pet)
Romano et al ²¹ (2002)	Yes (aminopenicillin or piperacillin)	173/259 (67%)	259/259 (100%)	94/259 (36%)	93/173 (54%)	93/173 (54%)	30	4 yr	Penicillin G 5% (pet) 5% (pet) Piperacilin 200 mg/ml (aq)
Romano et al ¹¹ (1995)	Yes (aminopenicillin)	60/195 (31%)	195/195 (100%)	33/195 (17%)	33/60 (55%)	33/60 (55%)	20	3 yr	5% (pet)
Lammintausta et al ²⁴ (2002)	Yes (clindamycin)	6/6 (100%)	6/6 (100%)	5/6 (83%)	5/6 (83%)	5/6 (83%)	22	9 weeks (2 weeks – 4 mo)	10% (pet) / ethanol 10–20% (pet) / (aq) 100% clindamycin
Barbaud et al ²² (2004)	Yes (pristinamycin)	18/29 (62%)	29/29 (100%)	20/29 (69%)	13/18 (72%)	13/18 (72%)	12	6 mo	10–30% (pet) / (aq)
Mayence et al ²³ (1999)	Yes (pristinamycin)	5/11 (45%)	11/11 (100%)	9/11 (82%)	3/5 (60%)	3/5 (60%)	30	1 – 3 mo	20% (pet) / (aq)
Gonçalo et al ¹⁶ (2000)	Yes (multiple)	66/66 (100%)	NR	29/66 (44%)	NR	NR	> 15	NR	5–10% (pet)
Barbaud et al ¹⁷ (1998)	Yes (multiple)	21/72 (29%)*	41/72 (57%)	27/72 (38%)	10/16 (63%)	10/16 (63%)	> 20	6 weeks	30% (pet) / (aq)
Lammintausta et al ¹⁴ (2005)	No	785/826 (95%)	80% (30/30)	89/826 (11%)	NR	NR	≥ 5	NR	20–30% (pet) / (aq)
Grandhe et al ¹⁸ (2004)	No	13/30 (43%)	30/30 (100%)	13/30 (43%)	6/13 (46%)	6/13 (46%)	20	(2 mo – 20 yr) For +PT: mean 1 yr For –PT: mean 6 yr	20% (pet)
Osawa et al ¹⁹ (1990)	No	NR	NR	62/197 (31%)	NR	NR	—	NR	20% (pet) / (aq)
Bruynzeel et al ¹⁵ (1987)	No	56/56 (100%)	NR	6/56 (11%)	NR	NR	20	NR	20% (aq)

* Subjects were selected for investigation only after patch test positivity was demonstrated.

† Patients with purpura and an exanthem were categorized separately from patients with exanthem only.

Abx = antibiotic; aq = water; d = days; EX = exanthem; mo = months; NR = not reported; pet = petrolatum; +PT = positive patch-test reactions; –PT = negative patch-test reactions; pts = patients; yr = years.

826 patients who had a suspected systemic drug allergy. Patients were tested with potential drug culprits, including antibiotics (80%), nonsteroidal antiinflammatory drugs, cardiovascular drugs, antiepileptics, and psychiatric drugs. The majority (95%) of the patients had a history of an exanthem (results for this group were not reported separately); the remainder had a history of urticaria, fixed drug eruption, vasculitis, erythema multiforme, or a photodermatosis. Overall, 11% of patients reacted to at least one systemic medication on patch testing. Almost all of these positive patients (81 of 89) had a history of an exanthem and 8 patients had a history of a fixed drug eruption. Patients were tested with up to four different drugs, which were diluted 20 to 30% in petrolatum or saline. The antibiotics that were used most frequently for testing were β -lactams, sulfonamides, and clindamycin (Table 3). The rates of positive reactions to each of these were 3.9% (39 of 1,008), 2.9% (15 of 518), and 19% (12 of 63), respectively. Reaction rates to benzylpenicillin, amoxicillin, and trimethoprim were 3.9% (6 of 152), 4%

(10 of 247), and 6.1% (10 of 163), respectively. Macrolides, tetracyclines, and quinolones were also tested in 160, 108, and 32 patients, respectively; no reactions occurred in any of these patients. This study included 20 negative control patients, none of whom reacted. The significance of these results, particularly for drugs with which a small number of patch tests were performed, is unclear because results were not listed separately for specific cutaneous reactions such as urticaria, vasculitic lesions, and fixed drug eruptions.

Gonçalo and colleagues¹⁶ patch-tested 66 patients (aged 12 to 83 years) with a history of a maculopapular rash to antibiotics (58%), antiepileptics (25%), allopurinol (11%), or other drugs (6%). Of 38 patch-test reactions, 15 (39%) were positive to antibiotics. The majority were due to penicillins (57% [12 of 21]); one in each case was due to cephalosporins (1 of 3), clindamycin (1 of 3), and espiramycin (1 of 2), and no reactions were seen to quinolones (2) and co-trimoxazole (7). More than 15 control patients for each drug had negative patch-test

Table 3. Frequency of Positive Patch-Test Reactions to Selected Antibiotics in Lammintausta and Kortekangas-Savolainen Study

<i>Drug Class</i>	<i>Antibiotic</i>	<i>Number of +PT in All Patients</i>	<i>%</i>
β -lactams	Phenoxymethyl penicillin	8/298	2.6
	Benzylpenicillin	6/152	3.9
	Amoxicillin	10/247	4.0
	Cloxacillin	1/3	33.3
	Meropenem	1/2	50.0
	Cephalosporin	13/306	4.2
	Cephalexin	3/173	1.7
	Cefadroxil	1/51	1.9
	Cefaclor	1/43	2.3
	Cefuroxime	4/29	13.8
	Ceftriaxone	4/10	40.0
Sulfonamides	Sulfamethoxazole (SMP)	1/215	0.4
	Trimethoprim (TMX)	10/163	6.1
	SMP +TMX	4/140	2.9
Macrolides	Erythromycin	0/129	0
	Azithromycin	0/27	0
	Roxithromycin	0/4	0
Tetracyclines	Doxycycline	0/76	0
	Tetracycline	0/32	0
Aminoglycosides	Gentamicin	1/2	50.0
Antituberculars	Isoniazid	1/2	50.0
Quinolones	—	0/32	0
Others	Clindamycin	12/63	19.0
	Metronidazole	1/15	6.7
	Nitrofurantoin	0/19	0

Adapted from Lammintausta.¹⁴

+PT = positive patch-test reaction.

reactions. The time interval between initial drug eruption and patch testing was not reported.

In a 1998 study conducted by Barbaud and colleagues,¹⁷ 72 patients (mean age, 52 years) underwent patch testing with antimicrobials (57%), cardiovascular drugs (11%), nonsteroidal antiinflammatory agents (4%), psychiatric drugs (4%), antiepileptics (3%), or other drugs (24%). Patients had a history of a maculopapular rash with or without purpura (8% with, 29% without), urticaria (25%), generalized eczema (11%), erythroderma (10%), fixed drug eruption (4%), or other drug rashes (13%). Sixty-three percent of patients (10 of 16) with a history of a maculopapular rash had patch-test reactions to antibiotics. Amoxicillin caused frequent reactions (5 of 8).

Grandhe and colleagues¹⁸ patch-tested 30 patients (aged 22 to 69 years) with 18 antibacterial agents: nine cephalosporins, five fluoroquinolones, penicillin G, amoxicillin, piperacillin, and co-trimoxazole. These patients had different cutaneous presentations, including maculopapular rash (43%), fixed drug eruption (27%), generalized eczema (20%), and urticaria (10%). Almost half of the patients with a history of a maculopapular rash (6 of 13) showed a positive reaction to at least one systemic antibiotic on patch testing. The results of testing with individual drugs were not reported separately. The mean interval between initial drug hypersensitivity and evaluation for positive patch-test results was 1 year; for negative patch-test results, it was 6 years. None of the 20 negative control patients had positive test reactions.

In a large study, Osawa and colleagues¹⁹ examined 197 patients (aged 1 to 85 years) with suspected systemic drug allergy. Patients underwent patch testing with antibiotics (penicillins, cephalosporins, and aminoglycosides; these caused 32% of all patch-test reactions), piroxicam (14%), anticonvulsants (13%), captopril (10%), gold salts (5%), and/or other drugs (26%). Patients had a history of maculopapular rash (37%), erythema multiforme (15%), generalized eczema (8%), erythroderma (7%), lichenoid drug eruption (6%), fixed drug eruption (3%), or other type of cutaneous eruption (24%). Only 14% of all patch-test reactions in patients with a history of a maculopapular rash were positive; 38% of all patch-test reactions in patients, regardless of rash type, were positive to antibiotics. The frequency of positive reactions for specific drug or specific rash type was not reported separately. The use of negative controls and the interval between the initial cutaneous eruption and patch testing were also not reported.

Finally, Bruynzeel and van Ketel¹⁵ evaluated only patients with a history of maculopapular rash from

numerous medications, including antibiotics. Overall, only 6 of 56 patients (11%) reacted on patch testing. Data were not reported separately for individual drugs. None of the 20 negative control patients were positive.

β-Lactams

Several investigators have examined the diagnostic feasibility of patch testing for the diagnosis of β-lactam sensitivity. Lisi and colleagues²⁰ selected 101 patients (aged 15 to 87 years) who reported a recurrence of a rash following the inadvertent administration of a β-lactam medication. This study included patients who had presented with urticaria (44%), a maculopapular rash (32%), anaphylaxis (13%), or an unspecified rash (11%). About a third of the patients with a history of maculopapular rash reacted on patch testing with amoxicillin, penicillin G, ampicillin, bacampicillin, or a cephalosporin (cephalexin, cephaloridine, or ceftriaxone). The authors noted that frequent reactions occurred with aminopenicillins (amoxicillin [8 of 46] and ampicillin [5 of 13]) but that none occurred with aztreonam. This study did not report the use of negative controls nor the duration of time between the initial cutaneous drug eruption and patch testing.

Romano and colleagues¹¹ evaluated patch testing with aminopenicillins in two studies. In the first study, 195 subjects (aged 13 to 86 years) with a history of an adverse cutaneous reaction to one or more aminopenicillins underwent patch testing; 31% of these subjects (60 of 195) had a history of a maculopapular rash; of these, 55% (33 of 60) had patch-test reactions to amoxicillin, ampicillin, or benzylpenicillin. In the second study, Romano and colleagues²¹ tested a different group of patients (259 patients aged 13–84 years) with benzylpenicillin, amoxicillin, and piperacillin. Two-thirds of these patients had a history of an exanthem (173 of 259 [67%]); of these, 54% (93 of 173) reacted on patch testing. Most of the patients (90 of 93) reacted to aminopenicillins. In both studies, the mean interval between the drug eruption and patch testing was 3 to 4 years. Both studies included at least 20 negative control patients, all of whom were patch test negative.

Barbaud and colleagues¹⁷ selected 72 patients (mean age, 52.3 years) with high drug imputability to a single drug. Of the 8 patients with a history of a maculopapular rash to amoxicillin, 5 (63%) had a positive patch-test reaction to the drug. Patch tests were performed 6 weeks after the cutaneous presentation. None of the negative

control patients (number not reported) reacted to the active drug, preservatives, or colorings.

We calculated a pooled reaction rate to aminopenicillins^{11,17,21} of 53% (Table 4). The greatest limitation in pooling these data is that there is a strong bias from the published data of one author.^{11,21} Romano and colleagues used a lower drug concentration (5% in both studies vs the 30% concentration in the study by Barbaud and colleagues), and patch testing was done years after the cutaneous reaction, as compared to 6 weeks in the study by Barbaud and colleagues.

Pristinamycin

Streptogramins (also called synergistin antibiotics) are characterized by their two chains, a depsipeptide and a macrocyclic lactone. Pristinamycin, virginiamycin, and dalbopristin-quinupristin belong to this drug class. Dalbopristin-quinupristin is approved by the US Food and Drug Administration for the treatment of vancomycin-resistant *Enterococcus faecium* bacteremia and for complicated skin infections caused by methicillin-resistant *Staphylococcus aureus* or *Streptococcus pyogenes*. The other two streptogramins are not available in the United States.

Patch testing with systemic pristinamycin has been documented in at least three studies. The largest study included 29 subjects (aged 16 to 93 years) who had a high drug imputability, defined as a drug eruption occurring after the recent introduction of pristinamycin or as two separate episodes of cutaneous drug eruption following exposure to oral pristinamycin.²² Patients underwent patch testing with pristinamycin, virginiamycin, or dalbopristin-quinupristin. Six months after the initial cutaneous drug eruption, 69% of all subjects tested (20 of 29) had positive patch-test reactions to pristinamycin, and 72% of patients (13 of 18) with a history of a

maculopapular rash reacted. None of the 12 negative control patients reacted. In a previously described smaller and separate study by Barbaud and colleagues,¹⁷ almost all of the patients tested (8 of 9 [89%]) had positive patch-test reactions to pristinamycin, and all 5 patients with a history of a maculopapular rash had a positive patch-test reaction.

Mayence and colleagues²³ also found a high frequency of positive patch-test reactions in a study of 11 patients (mean age, 51 years), most of whom had high drug imputability; 9 patients reacted to pristinamycin on patch testing, and 3 (60%) of the 5 patients with a history of a maculopapular rash reacted. None of the 30 negative control patients showed a response. The patch tests were performed 1 to 3 months after the initial eruption.

Pooled patch-test results from the above studies^{17,22,23} specifically for patients with a history of a maculopapular rash from streptogramins are listed in Table 4. Of patients who were tested, 75% (21 of 28) reacted. This unusually high reactivity may be explained by possible prior use of topical virginiamycin. In the report of Mayence and colleagues, 4 of the 11 patients had previously used topical virginiamycin.²³ Thus, it is possible that patients may be initially sensitized topically and then later exhibit a cross-reaction to a systemic agent in this drug class.

Clindamycin

Lammintausta and colleagues²⁴ selected six patients (aged 36–82 years) who had a strong history suspicious for clindamycin hypersensitivity. All presented with a history of a drug exanthem, and the majority (5 of 6) had positive patch-test reactions. Tests were performed as early as 2 weeks after the drug eruption, and all subjects were tested with clindamycin at 100% and/or clindamycin diluted 10 to 20% in both petrolatum and saline. None of the 22 negative control patients reacted.

Table 4. Pooled Data on Patch-Test Results for Selected Antibiotics

Antibiotic Class or Drug	No. of +PT in pts with MPR	Test Concentration and Vehicle	Study
Aminopenicillins	33/60	5% pet.	Romano et al ¹¹ (1995)
	90/173	5% pet.	Romano et al ²¹ (2002)
	5/8	30% pet./aq.	Barbaud et al ¹⁷ (1998)
	Total: 128/241 (53%)		
Pristinamycin	13/18	10–30% pet./aq.	Barbaud et al ²² (2004)
	5/5	30% pet./aq.	Barbaud et al ¹⁷ (1998)
	3/5	20% pet./aq.	Mayence et al ²³ (1999)
	Total: 21/28 (75%)		

aq. = water; MPR = maculopapular rash; pet. = petrolatum; +PT = patch-test reaction.

Validity and Predictive Value

The “gold standard” for confirming allergy to systemic medications is oral provocation. The use of oral challenge in comprehensive studies on the sensitivity and specificity of patch tests has been precluded by ethical concerns and the labor-intensive nature of this type of testing. A few studies have evaluated oral challenge with small groups of patients.

Romano and colleagues²¹ performed oral provocation tests with 50 mg of ampicillin or amoxicillin in most (64 of 80 [80%]) of their patch-test-negative patients with a history of a maculopapular rash thought to be due to aminopenicillins (Table 5). Only one patient developed a drug rash. Even if all of the remaining patients (16) who were not challenged were also positive, the calculated negative predictive value of patch testing would be still be at least 79%.

In their 1995 study, Romano and colleagues performed oral provocation with ampicillin or amoxicillin (administered in sequential doses of 5 mg, 50 mg, and 500 mg) in about half (18 of 33) of the patients who had a positive patch-test reaction and a history of a maculopapular rash.¹¹ All 18 of the orally challenged patients developed a maculopapular rash, and 10 patients also developed angioedema of the face and extremities within 6 to 24 hours. In addition, 59% of the patients (16 of 27) with a negative patch-test result and a history of a maculopapular rash were challenged, and none reacted. These results suggest a calculated negative predictive value of at least 59% and a sensitivity of at least 62%, based on worst-case scenarios (Table 6).

Patriarca and colleagues²⁵ patch tested thirty patients, who had at least one known patch test reaction to a β -lactam, to different antibiotics to evaluate cross-reactivity patterns. Systemic tolerance tests were also conducted.

Table 5. Calculated Negative Predictive Value for Patch Testing with Aminopenicillins in Patients with History of Maculopapular Rash

Patch Test	Oral Challenge*		Total No. Challenged
	Positive	Negative	
Positive	NP	NP	—
Negative	1 + (16)	63	64/80

Adapted from Romano et al.²¹

NP = not performed.

Negative predictive value at least 79%.

*50 mg ampicillin or amoxicillin.

(Hypothetical number for false negatives in worst case scenario for individuals who were not challenged orally.)

Table 6. Calculated Sensitivity and Specificity for Patch Testing with Aminopenicillins in Patients with a History of Maculopapular Rash

Patch Test	Oral Challenge*		No. Patch Tested
	Positive	Negative	
Positive	18	(15)	33
Negative	(11)	16	27

Adapted from Romano et al.¹¹

Sensitivity at least 62% and specificity at least 52%.

Positive predictive value at least 55%.

Negative predictive value at least 59%.

*5 mg, 50 mg, 500mg ampicillin or amoxicillin.

(Hypothetical number for false positives and false negatives in worst case scenarios for individuals who were not challenged orally.)

Overall, 4.8% of the oral challenge tests (12/252) were positive in the setting of negative patch tests, yielding a reported negative predictive value of 95%. Eleven patients consented to an oral challenge and all developed a maculopapular rash. The mean interval time between the original cutaneous adverse reaction and evaluation was six years.

Lammintausta and colleagues²⁴ challenged three patients who had a history of a drug exanthem (two were patch test positive, and 1 was patch test negative) with oral clindamycin at incremental doses of 37.5 mg, 75 mg, 150 mg, or 450 mg (Table 7). One of the two patients who had a positive patch-test result had no reaction on oral challenge with the 450 mg dose. The one patient with a negative patch-test result developed a symmetric macular rash after oral administration of 75 mg of clindamycin. Authors ascribed this false-negative patch-test reaction to the short interval (2 weeks) between the initial cutaneous eruption and patch testing. In this small study, at least one false positive and one false negative were demonstrated, and a single case of clindamycin hypersensitivity was confirmed by oral provocation.

In the 2005 study by Lammintausta and Kortekangas-Savolainen,¹⁴ 30% of patients (245 of 826) who had undergone patch testing underwent a systemic challenge. Twelve patch-test-positive patients with a history of a drug rash to antibiotics were challenged (data on the type of drug rash were not reported separately), and the majority (9 of 12) developed an exanthem. The three false positive patch tests occurred to trimethoprim, clindamycin and metronidazole. Also challenged were 207 patch test negative patients with a history of a drug rash to antibiotics (data on type of drug rash were not reported separately), and false negative patch test reactions occurred in 11 (5%). Oral provocation reinduced an exanthem in 6

Table 7. Results of Oral Challenge Tests in Selected Patients with a History of Cutaneous Drug Eruption

Study	Dosage	Oral Challenge Test			
		Total No. challenged	In patients with +PT (%)	No. of FP	In patients with -PT (%) No. of FN
Lammintausta et al ²⁴ (2002)	37.5 mg, 75 mg, 150 mg, or 450 mg clindamycin	3/6	2/5 (40%)	1	1/1 (100%) 1
Lammintausta, Kortekangas-Savolainen ¹⁴ (2005)	Multiple drugs at 10–25% normal dose and increased to full dose	245/826*	16/89 (18%)	3	229/737 (31%) 22

FN = false negative; FP = false positive; +PT = positive patch-test reaction; -PT = negative patch-test reaction.

* Includes patients who were patch tested with all drugs investigated and regardless of drug rash type.

patients: amoxicillin (2 cases) and one case of each penicillin, co-trimoxazole, clindamycin, and metronidazole. In this study, drug challenges were started at 10 to 25% of the regular dose and then doubled until a standard dose was achieved.

Although they did not perform a formal oral provocation test, Barbaud and colleagues¹⁷ reported that of the 41 patients in their 1998 study who underwent patch testing for antibiotics, 5 patients with a history of a maculopapular rash inadvertently received the responsible drug during subsequent medical care. All 5 patients developed a rash on rechallenge; 3 were patch test positive (amoxicillin), and 2 were patch test negative (co-trimoxazole and isoniazid).

Osawa and colleagues¹⁹ also performed oral challenge tests; however, the data were not reported such that false positives and negatives could be determined. These authors compared ratios of positive patch-test reactions to ratios of positive results on oral provocation; 38% of patch-test reactions (23 of 60) were positive with antibiotics, and a similar percentage of patients (33% [4 of 12]) reacted to an oral challenge.

Laboratory Correlations

Several studies have evaluated patients with positive patch-test results by in vitro testing and/or histopathology. In one study, 17 patients who had positive patch-test reactions to penicillin and a history of either a maculopapular rash or urticaria underwent lymphocyte transformation tests. Lymphocytes from most patients (14 of 17) showed increased deoxyribonucleic acid synthesis after in vitro exposure to penicillin G and ampicillin.²⁶ Immunohistochemical studies showed perivascular mononuclear infiltrates with CD4⁺ and CD8⁺ cells from skin biopsy specimens from patients with positive patch-test results, suggesting that the cutaneous drug reactions were

due to a delayed hypersensitivity reaction.²⁷ In another study, biopsy specimens of reactions from the patch-tested skin of four patients with positive patch-test reactions to aminopenicillins showed perivascular lymphocyte-eosinophil infiltrates and epidermal spongiosis, consistent with a delayed-type hypersensitivity reaction.¹¹

Association of Drug Rash Type and Patch Testing

We calculated pooled risk ratios and found that, overall, patients with a history of a maculopapular rash from antibiotics were 2.9 times more likely to have a positive patch-test result than those with a history of other types of drug rashes ($p < .001$) (Table 8). Patients with a history of a maculopapular rash to aminopenicillins or β -lactams had calculated risk ratios of 46.2 ($p < .001$)²¹ and 2.0 ($p = .078$),²⁰ respectively. In contrast, data from the 2005 study by Lammintausta and Kortekangas-Savolainen which included patients with a maculopapular rash to any drug, found that patients with a history of a maculopapular rash were half as likely to have a positive patch-test reaction than patients with a history of other types of rashes ($p = .064$). This difference may be explained by the inclusion of patients with rashes to drugs other than antibiotics and variations in study design.

Cross-Reactivity of Antibiotics in Patch Testing

Several studies have evaluated the cross-reactivity of antibiotics in patch testing. Lammintausta and Kortekangas-Savolainen¹⁴ reported five patients who reacted to both benzylpenicillin and phenoxymethyl penicillin, one patient who reacted to both cefuroxime and ceftriaxone, and another patient who reacted to cephalexin, cefadroxil, and cefaclor. In a separate study,¹⁸ 30 patients were patch-tested with multiple antibiotics but only one reacted to both cefadroxil and amoxicillin. In the

Table 8. Associations of Drug Rash Type and Patch-Test Result

Study	Drug Class	Rash Type	No. of Patients with Patch Test Result		Calculated Measures of Association		
			Positive	Negative	Chi-Square, p value (95% CI)	Odds Ratio (95% CI)	Relative Risk (95% CI)
Romano et al ²¹ (2002)	Aminopenicillins & piperacillin	MPR	93	80	$p < .001^{\Phi}$	98.81 (13.45 – 725.78)	46.23 (6.55–326.07)
Lisi et al ²⁰ (1997)	β -lactams	Non-MPR	1	85			
		MPR	10	22	$\chi^2 = 3.11, p = .078$		1.96 (0.93–4.14)
Mayence et al ²³ (1999)	Pristinamycin	Non-MPR	11	58	$2.40 (0.89 – 6.43)$		
		MPR	3	2	$p = .182^{\Phi}$		–
Barbaud et al ²² (2004)	Pristinamycin	Non-MPR	6	0			
		MPR	13	5	$p = .694^{\Phi}$	1.49 (0.30 – 7.39)	1.13 (0.67–1.93)
Barbaud et al ¹⁷ (1998)	Antibiotics	Non-MPR	7	4			
		MPR	10	6	$\chi^2 = 4.78, p = .029$		2.23 (1.07–4.65)
Grandhe et al ¹⁸ (2004)	Antibiotics	Non-MPR	7	18	$4.29 (1.13 – 16.31)$		
		MPR	6	7	$\chi^2 = 0.07, p = .785$		1.12 (0.50–2.54)
Lammintausta, Kortekangas-Savolainen ¹⁴ (2005)	All drugs (80% are Abx)	Non-MPR	7	10	$1.22 (0.29 – 5.26)$		
		MPR	81	704	$\chi^2 = 3.43, p = .064$		0.53 (0.27–1.02)
Pooled from above studies ^{17,18,20–23}	Antibiotics	Non-MPR	8	33	$0.47 (0.21 – 1.06)$		
		MPR	135	122	$\chi^2 = 58.99, p < .001$		2.88 (2.12–3.19)
Pooled from all of the above studies ^{14,17,18,20–23}	All drugs	Non-MPR	39	175	$4.97 (3.25 – 7.59)$		
		MPR	116	826	$\chi^2 = 6.38, p = .012$		0.67 (0.49–0.91)
		Non-MPR	47	208	$0.62 (0.43 – 0.90)$		

Abx = antibiotics; CI = confidence interval; MPR = maculopapular.

All tests presented in this table were Pearson chi-squared tests with 1 degree of freedom, except those notated by Φ , which were Fisher's exact tests.

2002 study by Romano and colleagues,²¹ all of the 94 patients who were patch-tested with either ampicillin or amoxicillin had positive reactions to both, indicating significant cross-reactivity. Of the patients patch-tested with pristinamycin in the 2004 study by Barbaud and colleagues,²² 9 of 22 patients (41%) reacted to virginiamycin and 7 of 8 (88%) reacted to dalfopristin-quinupristin. In a case report by Pérez Pimento and colleagues,²⁸ a patient with a history of maculopapular rash had positive patch-test reactions to both aztreonam 20% pet. and ceftazidime 20% pet. but negative results on oral challenge tests with amoxicillin, amoxicillin-clavulanate, and three cephalosporins at therapeutic dosages.

Patriarca and colleagues²⁵ performed patch tests and oral challenge tests with aminocephalosporins on 11 patients who had a history of a maculopapular rash to an aminopenicillin that was confirmed previously on patch testing. All of the patients were patch test negative to the aminocephalosporins, and only one of the patients developed an exanthem from an oral challenge to cephalexin, an aminocephalosporin. This suggested that cross-reactivity between aminopenicillins and aminocephalosporins may be rare. No cross-reactivity was found between aminopenicillins and either monobactams and carbapenems.

Reproducibility of Patch-Test Results in Evaluating Drug Eruptions

It is generally recognized that patch-test reactivity can fluctuate with time. New reactions may arise, and previously positive reactions may also disappear. Not surprisingly, this phenomenon of the “twinkling back”²⁹ has also been reported with regard to patch testing with systemic medications. Bruynzeel and van Ketel³⁰ retested 15 patients who had positive patch-test reactions to amoxicillin, phenethicillin, or ampicillin; the retesting was done at 10, 16, 64, and 100 weeks after the initial cutaneous manifestation, with the original drug culprits plus penicillin G, cloxacillin, cefadrin, and cephalothin. Eight of 15 patients showed more positive reactions over time, and all but one developed more intense reactions. Five patients, however, had fewer reactions and exhibited milder reactions. Two patients were negative upon retesting. None of the negative control patients reacted during the retesting period.

Romano and colleagues³¹ found a similar pattern when they repeated patch tests on 23 patients who had had an initial eruption of urticaria, angioedema, or maculopapular rashes from ampicillin, amoxicillin, or penicillin over

time. Four patients showed an increased severity of reactions at 18 months, 4 years, 6.5 years, and 7.5 years later, respectively. Two patients who were initially allergic only to amoxicillin developed new reactions to penicillin. Sixteen patients exhibited patch-test results similar to those of the initial testing. Two patients showed decreased reactivity to ampicillin at 4.5 years and 2 years, respectively. No patients were completely negative on retesting.

Risks of Patch Testing with Systemic Antibiotics

Similar to patch testing with other antigens, patch testing with antibiotics is generally safe. In a large study of 826 patients involving patch testing with various drug classes, including antibiotics, only 2 patients were sensitized *de novo* to a β -lactam.¹⁴ One patient developed systemic symptoms during testing with pseudoephedrine 20% in petrolatum and/or saline. Of 72 patients, 5 developed “a slight relapse” of the original cutaneous adverse drug reaction (not described, but assumed to be a recall reaction) when patch-tested with acyclovir, amoxicillin, hydroxyzine, pseudoephedrine, or triamcinolone.¹⁷ There have been similar and isolated reports of recall reactions when patch testing was performed with carbamazepine,³² pseudoephedrine,^{17,33,34} clobazepam,³⁵ metamizole,³⁶ and paracetamol (acetaminophen).³⁷ In the study conducted by Grandhe and colleagues,¹⁸ none of the 30 patients who were patch-tested with antibiotics reported side effects.

Anaphylactic reactions have been reported during patch testing with propyphenazon (a pyrazolone nonsteroidal antiinflammatory agent),³⁸ diclofenac 1% pet,³⁹ topical neomycin,^{40,41} chloramphenicol,⁴² and penicillin.^{43,44} Clinical details and data on patch-test drug concentrations and vehicles were not available for these reports.

Patch-Testing Considerations for the Evaluation of Drug Eruptions

There are several important factors to consider when evaluating patients with a cutaneous drug eruption from a systemic medication. First, it is important to realize that patients may have more than one type of hypersensitivity reaction, so other skin tests (intradermal and skin-prick tests) should also be performed.

Second, an allergy to ingredients other than the active drug may also be present; preservatives and/or other inert fillers in medications^{45,46} (such as benzyl alcohol, chlor-

ocresol, parabens,⁴⁷ and sodium lauryl sulfate⁴⁸) have been reported to cause reactions.

Third, drug eruptions may be enhanced or modified by a concomitant infection or a drug-drug interaction. For example, transient maculopapular rashes have been reported in patients who are infected with human immunodeficiency virus and have *Pneumocystis carinii* pneumonia during treatment with clindamycin and primaquine. These rashes resolved in 3 to 5 days despite continuation of the drug combination.⁴⁹ Amoxicillin and Epstein-Barr viral disease states are well known to cause drug exanthems. Drug-drug interactions may occur, such as with sulfamethoxazole and trimethoprim. One patient had negative patch-test results for sulfamethoxazole and trimethoprim tested separately, developed a drug exanthem after an oral challenge with the combination of these two drugs.¹⁴ This finding does not exclude the possibility that patch testing itself may have failed to uncover a true drug hypersensitivity.

Fourth, the success of patch testing depends on the ability of the drug to penetrate the epidermis. A number of reports have indicated that intradermal tests may be more sensitive than patch tests, perhaps because of the direct deposition of haptens into the dermis.²¹

Fifth, the optimal concentrations and vehicles for testing systemic drugs are largely unknown. One patient reacted to patch testing only with a drug diluted in petrolatum, not diluted in water or tested "neat."¹⁷ Certain drug concentrations or hydrogen ion concentration (pH) values⁴⁸ may also cause irritant reactions; hence, human negative controls are crucial for interpreting test results.

Perhaps the most perplexing and inherent problem with patch testing is that a drug metabolite, rather than the drug, may be the responsible hapten. The frequency of a drug metabolite causing an allergic response is unknown. In this situation, patch testing may be futile.

Limitations of This Review

In conducting this review, we were challenged by the diversity of study designs and methodologies. Whereas a few studies focused solely on maculopapular eruptions, most included all types of cutaneous drug eruptions, including urticaria, fixed drug eruptions, and even acute generalized exanthematous pustulosis. The classification of these reactions was likely limited by recall bias as few studies reported clinical documentation by a dermatologist at the initial cutaneous drug eruption. From our personal communication with one of the authors,¹⁴ only a minority

of the patients (about 5%) in the study were evaluated by a dermatologist at the time of the initial drug rash, (Kaija Lammintausta, personal communication, September 2005). In most studies, either patients were selected because they had a history of a drug eruption or restricted to those with a high imputability to a single drug. Also, selection bias was likely in studies which orally challenged only a subset of patients. Different vehicles and variable drug concentrations were also used in different studies, and the time interval between drug eruption and evaluation was highly variable, ranging from a few weeks to several years. Our calculations of sensitivity, specificity, and predictive values of patch tests are limited by small samples, and calculated pooled risk ratios are likely biased by the results of large studies. Finally, only manuscripts in English were reviewed; consequently, important foreign studies^{50,51} may have been missed.

Summary

Patch testing may have a diagnostic role in the evaluation of exanthems due to systemic antibiotics. The frequency of positive patch-test reactions in these cases varies between 31% and 83% and is higher for certain antibiotics, especially aminopenicillins and pristinamycin. Calculations of pooled results indicate that patients with a history of an exanthem due to antibiotics are more likely to have a positive patch-test reaction than are patients with a history of other types of drug rashes. From studies reporting results of oral provocation, our calculations indicate that patch testing has a reasonable negative predictive value, especially for aminopenicillins (59–79%), although sensitivity and specificity may be lower (62% and 52%, respectively).

It is unclear if the use of patch testing for the diagnosis of cutaneous drug reactions to systemic antibiotics will alter the clinical management of patients. Patch testing may have the greatest clinical impact in situations where there is no therapeutic equivalent to the drug in question (such as antituberculous drugs) or when the drug in question is expected to be used in the future. Isogai and colleagues cleverly used patch testing to show that bacampicillin hydrochloride was the cause of a pustular eruption, rather than an acute exacerbation of a preexisting pustular dermatosis.⁵²

More evidence is needed before routine patch testing with systemic antibiotics for the diagnosis of drug eruptions can be recommended. Future studies should examine whether patch testing influences health outcomes and how the selection of patients with a high pretest

probability for reaction to one or more drugs changes the efficacy of this test. Although laboratory research has offered clinicians a glimpse of the pathologic mechanisms of drug exanthems, more studies are needed to elucidate the exact mechanism and antigen (the active drug or a metabolite) involved. Research on the appropriate vehicle and concentration for patch testing with these drugs is also crucial. Ultimately, large-scale trials may be necessary before patch testing is widely accepted as a routine tool in the diagnosis of systemic drug hypersensitivity.

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