

Delayed Patch-Test Reading After 5 Days: An Update From the Mayo Clinic Contact Dermatitis Group

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Background: Patch-test readings after day 5 have previously been used to identify delayed reactions to metals and topical antibiotics.

Objective: The aims of this study were to identify allergens for which late readings (beyond day 5) would be most valuable and to compare our results with our previous study on delayed patch-test readings.

Methods: This was a retrospective study of 298 patients who underwent metal and corticosteroid series patch testing from January 1, 2007, through December 31, 2013. Patch-test readings were conducted on days 3 and 5 and at least once sometime between days 7 and 14. All reactions were examined at each reading.

Conclusions: These results were concordant with our previous findings that additional readings after day 7 are particularly useful for identifying reactions to metals (gold, cobalt, beryllium, palladium), specific preservatives (dodecyl gallate, propolis), and the topical antibiotic neomycin. New delayed reactions to bacitracin, *p*-phenylenediamine, and topical corticosteroids were not seen in this cohort.

We have previously investigated the utility of patch-test readings beyond day 5 and determined whether reactions are missed when delayed readings are not performed.¹ We found that readings beyond day 5 were useful for patients with suspected allergies to metals and topical antibiotics. However, delayed readings were of limited value for identifying delayed hypersensitivity to topical corticosteroids and *p*-phenylenediamine (PPD).

At our institution, readings are conducted on a 5-day schedule, with additional readings on days 7 through 14 for select allergens. Some studies on late patch-test reactions commonly define late readings as occurring after day 3 or 4,^{2–4} whereas in others, the delayed reading period begins at day 7.^{3–6}

Here, we update our previous study by reporting findings of delayed patch testing in a new cohort of patients. Our testing protocol now includes a request that patients undergoing patch testing to metals return for further reading of all their patch-test reactions

after day 5. In this report, we compare our findings to those of our previous study and those reported in the recent literature.

METHODS

Patients

We obtained approval for this study from our institutional review board. Written informed consent was obtained at the time of patch testing from all patients, before their inclusion in the study. We then retrospectively reviewed patch testing results of 298 patients seen from January 1, 2007, through December 31, 2013. Patients who had been patch tested to our metal and corticosteroid series were identified from a clinical database. Similar to our previous study, patients did not have any characteristics that could confound patch-test interpretation, including application of corticosteroids to test sites, treatment with immunosuppressant medications, or comorbid medical conditions that would affect the evaluation.¹

Patch-Test Application and Interpretation

Our methods for patch-test application and reading were similar to those of the North American Contact Dermatitis Group.^{7,8} Finn Chambers on Scanpor tape (Epitest Ltd Oy) were used for patch testing. Allergens were purchased from Chemotechnique Diagnostics, AllergEAZE (SmartPractice, Phoenix, AZ), or our institutional pharmacy.

Patch tests were placed on the upper back and remained for 48 hours. Patients returned on day 3 for removal of allergens. All patients underwent patch-test interpretations on day 3, day 5, and

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once again between days 7 and 14. At each reading, all reactions were examined (not only the reactions to metals or corticosteroids). This schedule was comparable to that in our previous study; however, in the current study, later readings were conducted between days 7 and 14, rather than through day 21.¹

Results were interpreted by using criteria similar to those of the North American Contact Dermatitis Group. Based on the presence of vesicles, papules, spreading edema, and bullae, patch-test reactions were classified as negative reaction, macular erythema, weak reaction, strong reaction, extreme reaction, or irritant reaction.^{8,9} Reactions that were weak, strong, or extreme were interpreted as positive reactions. Macular erythema reactions were determined to be positive reactions if the clinical context was appropriate.^{8,10}

RESULTS

A total of 29,775 individual reactions to 470 allergens were interpreted on day 5 and then again between days 7 and 14 for 298 patients. During the 7-year study period, new allergens were added to our series; therefore, not all patients were tested to every allergen. To avoid the effects of smaller sample sizes, we restricted our analysis to the 165 allergens that had been tested in at least 50 patients (25,043 individual reactions). Of these 165 allergens, 106 had reactions that differed between the initial and delayed readings. Among these 106 allergens, 44 allergens showed negative reactions on day 5 but positive reactions on day 7 or later (Table 1).

Eleven allergens caused delayed positive reactions (positive on days 7–14) that affected at least 2% of patients (Table 1). Of the 25,043 individual patch tests applied, 15,761 negative reactions were observed on day 5. However, 114 positive reactions (0.7%) on days 7 through 14 were observed after negative reactions on day 5. Allergens with the highest percentage of delayed positive reactions after day 5 were 2% gold sodium thiosulfate (newly positive reactions in 9/154 patients), 0.5% gold sodium thiosulfate (11/247 patients), and 0.25% dodecyl gallate (6/143 patients).

Most late-reacting allergens (29/44 [66%]) resulted in relevant macular erythema reactions (Table 1). Weak reactions were also common, occurring among 27 late-reacting allergens. Strong late reactions were rare and were observed for only 4 allergens (0.25% ammonium tetrachloroplatinate, 1% cobalt [II] hexahydrate, 2% gold sodium thiosulfate, 0.5% potassium dichromate). Only 1 extreme reaction occurred after day 7 (1% silver nitrate).

DISCUSSION

This study shows the utility of delayed patch-test readings after day 7 for metals (gold, beryllium, cobalt, potassium dicyanoaurate, palladium) and preservatives (dodecyl gallate, propolis). With regard to topical antibiotics, delayed positive reactions were seen for neomycin but not bacitracin. Delayed positive reactions to neomycin did not affect at least 2% of patients and therefore it was not listed in boldface type among the most common allergens causing late reactions in Table 1. Nevertheless, our study shows that reactions to most allergens

other than metals, preservatives, and the topical antibiotic neomycin are detectable with readings through day 5.

Comparison to Our Previous Study

As observed previously,¹ readings after day 5 have the most clinical utility if an allergy to metals or the topical antibiotic neomycin is suspected. In our prior study, preservatives (dodecyl gallate, thimerosal, methenamine) were associated with late reactions, and late reactions with dodecyl gallate were confirmed in the current study (propolis is a more recent addition to our allergen series). In contrast to our previous study, we did not observe late reactions to bacitracin, and methenamine and thimerosal were excluded because they were not tested in at least 50 patients.

In addition, our previous study showed that reactions to PPD and corticosteroids occur infrequently after day 5. Comparably, we found no newly positive reactions to PPD or to topical corticosteroids, including 0.01% budesonide, 1% clobetasol-17-propionate, 1% hydrocortisone-17-butyrate alcohol, and 1% triamcinolone acetonide. Therefore, this study is consistent with our previous finding that delayed readings provide limited information for suspected allergies to PPD and corticosteroids.

Delayed Reactions in the Literature

Recent studies on delayed patch testing reactions are outlined in Table 2. Because of the various methods used (eg, schedule of patch testing, definitions of late reactions), comparing results of the current study with other reports is somewhat challenging. However, many studies similarly defined a late reaction as that occurring at day 7 or later. Some series selected patients with specific medical conditions (eg, oral lichen lesions, eczema, arthroplasty) for patch testing,^{2,16,18} and several studies^{4,11,12,15} include self-reported late reactions instead of having reactions interpreted during scheduled readings. Nevertheless, we attempt to compare our findings with regard to delayed reactions to metals, topical antibiotics, corticosteroids, and PPD to those of previous reports.

Metals

Our findings that late readings were useful for the detection of reactions to metals are consistent with those in the literature. In their study of contact allergy to dental materials in patients with oral lichenoid lesions, Ahlgren et al² reported that late reactions occurred most commonly to the metals mercury, nickel, cobalt, and gold. The authors did not include a day 5 reading, although they did note a statistically significant increase in positive reactions on day 7 compared with day 3. Thomas et al¹⁸ studied contact allergies in patients with a history of arthroplasty. They reported that day 6 readings were particularly useful because of the higher frequency of newly positive reactions to nickel, colophonium, and potassium dichromate. In addition, Gawkrödger and Paul¹⁵ described 1 patient with a late (day 10) reaction to mercury with repeat patch testing. One patient in their series also had a questionably positive reaction to nickel on day 14 during initial patch testing. Higgins and Collins³ also identified

TABLE 1. Allergens Causing Delayed Positive Reactions

Allergens	Neg Day 5, Positive Day ≥ 7 (Delayed Pos Reactions)*†						
	Patients Tested, n	Patients With Positive Reactions, n (%)	Patients With Relevant Reactions, n (%)‡	Reaction Strength on Day ≥ 7			
				Relevant Macular Erythema, n (%)‡	Weak Reactions, n (%)‡	Strong Reactions, n (%)‡	Extreme Reactions, n (%)‡
0.1% 1,6-Hexanediol diacrylate	163	1 (0.6)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
2% 2-Hydroxypropyl methacrylate	163	1 (0.6)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
1% 4-tert-Butylphenol formaldehyde resin	124	1 (0.8)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
5% Amalgam	184	1 (0.5)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
5% Amalgam, nongamma 2	107	1 (0.9)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
Amidoamine 0.1% aq	115	1 (0.9)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
Ammonium tetrachloroplatinate 0.25% aq	287	2 (0.7)	1 (50)	1 (50.0)	0 (0)	1 (50.0)	0 (0)
Benzalkonium chloride 0.1% aq	121	1 (0.8)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
1% Benzoyl peroxide	185	1 (0.5)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
Beryllium sulfate tetrahydrate 1% aq	87	3 (3.4)	3 (100)	1 (33.3)	2 (66.7)	0 (0)	0 (0)
0.6% Black rubber mix	124	1 (0.8)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)
5% R-(L)-carvone	132	1 (0.8)	0 (0)	0 (0)	1 (100)	0 (0)	0 (0)
1% Chromium (III) chloride	189	1 (0.5)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
2.5% Cobalt (II) sulfate	188	1 (0.5)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
Cobalt (II) hexahydrate 1% in pet	292	7 (2.4)	6 (85.7)	4 (57.1)	2 (28.6)	1 (14.3)	0 (0)
1% Cobalt sulfate	85	3 (3.5)	2 (66.7)	2 (66.7)	1 (33.3)	0 (0)	0 (0)
1% Disperse blue 124	96	2 (2.1)	2 (100)	1 (50.0)	1 (50.0)	0 (0)	0 (0)
0.25% Dodecyl gallate	143	6 (4.2)	6 (100)	3 (50.0)	3 (50.0)	0 (0)	0 (0)
1% Epoxy resin	239	1 (0.4)	1 (100)	0	1 (100)	0 (0)	0 (0)
2% Ethylene glycol dimethacrylate	190	3 (1.6)	3 (100)	2 (66.7)	1 (33.3)	0 (0)	0 (0)
Formaldehyde 1% aq	124	1 (0.8)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
Gold chloride 0.5% alc	85	1 (1.2)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
Gold sodium thiosulfate 0.25% in pet	88	3 (3.4)	3 (100)	2 (66.7)	1 (33.3)	0 (0)	0 (0)
0.5% Gold sodium thiosulfate	247	11 (4.5)	11 (100)	7 (63.6)	4 (36.4)	0 (0)	0 (0)
2% Gold sodium thiosulfate	154	9 (5.8)	6 (66.7)	4 (44.4)	4 (44.4)	1 (11.1)	0 (0)
5% Lidocaine	229	1 (0.4)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
0.1% Mercuric chloride	288	3 (1.0)	3 (100)	3 (100)	0 (0)	0 (0)	0 (0)
0.5% Mercury	288	3 (1.0)	3 (100)	3 (100)	0 (0)	0 (0)	0 (0)
1% Mercury ammonium chloride	288	1 (0.3)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
5% Molybdenum	192	1 (0.5)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
20% Neomycin sulfate	123	1 (0.8)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
2.5% Nickel sulfate hexahydrate	292	3 (1.0)	2 (66.7)	0 (0)	3 (100)	0 (0)	0 (0)

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TABLE 1. (Continued)

Allergens	Neg Day 5, Positive Day ≥ 7 (Delayed Pos Reactions)*†						
	Patients Tested, n	Patients With Positive Reactions, n (%)	Patients With Relevant Reactions, n (%)‡	Relevant Macular Erythema, n (%)‡	Reaction Strength on Day ≥ 7		
					Weak Reactions, n (%)‡	Strong Reactions, n (%)‡	Extreme Reactions, n (%)‡
2% Palladium chloride	287	6 (2.1)	6 (100)	6 (100)	0 (0)	0 (0)	0 (0)
16% Paraben mix	124	1 (0.8)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
0.25% Potassium dichromate	138	2 (1.4)	2 (100)	1 (50.0)	1 (50.0)	0 (0)	0 (0)
0.5% Potassium dichromate	287	5 (1.7)	5 (100)	3 (60.0)	1 (20.0)	1 (20.0)	0 (0)
Potassium dicyanoaurate	288	9 (3.1)	9 (100)	5 (55.6)	4 (44.4)	0 (0)	0 (0)
0.1% aq							
10% Propolis	166	4 (2.4)	4 (100)	4 (100)	0 (0)	0 (0)	0 (0)
1% Quaternium 15	124	1 (0.8)	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
Silver nitrate 1% aq	288	2 (0.7)	2 (100)	1 (50.0)	0 (0)	0 (0)	1 (50.0)
2% Tetraethylene glycol dimethacrylate	184	1 (0.5)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
1% Thiuram mix	124	1 (0.8)	1 (100)	1 (100)	0 (0)	0 (0)	0 (0)
Ticonium as is	161	2 (1.2)	2 (100)	0 (0)	2 (100)	0 (0)	0 (0)
Vitallium as is	160	3 (1.9)	3 (100)	3 (100)	0 (0)	0 (0)	0 (0)

*Tests were read within 14 days after application.

†Allergens were tested in 50 or more patients. Weak reactions were defined as nonvesicular, erythema, infiltrated, or questionable papules. Strong reactions were edematous or vesicular. Extreme reactions were spreading, bulbous, or ulcerative. Boldface type designates allergens that caused delayed positive reactions for at least 2% of patients tested with that allergen.

‡Percentages were calculated using the number of patients with day ≥ 7 positive reactions as the denominator.

alc, alcohol; aq, aqueous; Neg, negative; pet, petrolatum; Pos, positive.

late reactions to mercury and cobalt chloride for 2 patients each out of 26 patients with newly positive reactions on day 7.

Topical Antibiotics

Late reactions to topical antibiotics have been reported in the literature. Madsen and Andersen¹⁶ reported that neomycin, hydrocortisone-17-butyrate, and budesonide were among those allergens for which delayed readings were most valuable because at least 10% of positive reactions would have been missed. The authors defined a late reaction as a positive reaction occurring on day 6 or 7 after a negative or doubtful reaction on day 3. Therefore, it is possible that with a day 5 reading, reactions to neomycin would have been found before day 6 or 7 in their study. Gawkrödger and Paul¹⁵ described a patient with a self-reported late (day 14) reaction to neomycin after initial patch testing. Reactions to gentamicin have also been reported.^{3,18} Gentamicin was not included in our series, but this finding is consistent with those from other studies, including another from our institution, which have reported late reactions to topical antibiotics.

Corticosteroids

Although we have found that late patch-test readings have limited value for the detection of corticosteroid reactions, some studies in the literature have reported delayed reactions to corticosteroids.^{1,19} As stated previously, Madsen and Andersen¹⁶ reported that the second

and third most common allergens causing newly positive late reactions were topical corticosteroids. Isaksson⁵ also reported 2 patients with clinically relevant late reactions to topical corticosteroids. Conversely, Higgins and Collins³ did not detect any newly positive reactions to corticosteroids in late readings in their series of 203 patients.

p-Phenylenediamine

With regard to reactions to PPD, studies at our institution, including the current study, have not found value in delayed readings; the literature is inconsistent with regard to PPD and delayed readings. Higgins and Collins³ did not detect late reactions to PPD. Hillen et al⁴ assessed the occurrence of late reactions to PPD in different concentrations and reported delayed reactions in 8 of 1666 patients with PPD concentrations of 0.5% and 0.4% but no late reactions at a concentration of 0.35%. They proposed that late reactions to PPD may be concentration dependent. Madsen and Andersen¹⁶ observed delayed reactions to PPD in 44 (22%) of the 201 total positive reactions to PPD. Active sensitization to PPD has also been reported.^{11,15}

Preservatives

We observed delayed reactions with the preservatives dodecyl gallate and propolis. Other studies have also identified late patch-test reactions to various preservatives. Madsen and Andersen¹⁶

TABLE 2. Review of the Recent Literature Addressing Late or Delayed Patch Testing

Study	Allergens	No. Patients	Days of Patch-Test Interpretation	Predefined Day of Late Reaction	Findings
Aalto-Korte et al, ¹¹ 2007	Large series of allergens	884	Days 2–4; days 2–5; or days 2, 3, and 6, depending on date of application Patients reported late reactions Patients with delayed reactions were retested to look for active sensitization	Day 10 or later	16 Patients reported late reactions; 11/12 patients with late reactions who were retested showed active sensitization (1.3% of all patients tested) Allergens that most commonly caused active sensitization were PPD and the Compositae extracts elecampane and black-eyed Susan
Ahlgren et al, ² 2014	Institution's "lichen series" (66 allergens from dental and cheilitis series)	83 with biopsy-proven oral lichen lesions	Days 3 and 7	Day 7	26/129 Reactions (20.2%) seen only on day 7 Metals (mercury, nickel, gold, and cobalt) most commonly caused late reactions Patch testing in patients with oral lichen lesions should include readings on day 3 or 4 and day 7
Davis et al, ¹ 2008	Large series of allergens	371	Days 3 and 5, and at least once during days 7–10 For metals, read at least once during days 10–14 and occasionally on day 21	—	Late readings were useful for reactions to metals (gold, palladium, beryllium, nickel, cobalt) and topical antibiotics (neomycin, bacitracin) Readings after day 5 were not useful in the diagnosis of reactions to other allergens (PPD and topical corticosteroids)
Barbuzza et al, ¹² 2008	Leather-related materials and standard hapten series	1	Days 2–4 Patient reported on day 10	After day 4	New reaction on day 10 to 1% dichlorophen G4 If late patch-test readings are not feasible, patients can be advised to watch for new lesions in patch-test sites
Lucas Costa et al, ¹³ 2008	Case 1: Spanish baseline series and a metal series Case 2: same as case 1 plus a series of rubber allergens	2	Days 2, 4	After day 10	Returned at day 15 (case 1) and 1 mo (case 2) after initial testing with new lesions where metal allergens were applied Repeat testing in both patients: pos reaction on days 2 and 4 to beryllium chloride 1% pet
Frick-Engfeldt et al, ¹⁴ 2007	Isocyanates at different concentrations: polymeric MDI 4,4'-MDI 4,4'-MDA	12 subjects, 20 controls	Days 4, 7, 11, 14, 18, 21, 25	After day 7	Late reactions were observed for 4,4'-MDA, 4,4'-MDI, and MDI products Approximately 38%–67% of pos reactions would have been missed if readings were conducted only through day 4 (4/6 patients for 4,4'-MDI; 4/7 for Pedilen; 3/8 for Desmodur; 3/5 for Lupranat*)

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TABLE 2. (Continued)

Study	Allergens	No. Patients	Days of Patch-Test Interpretation	Predefined Day of Late Reaction	Findings
Gawkrodger and Paul, ¹⁵ 2008	Series of allergens, unspecified	2000 total Analyzed 11/14 patients with late reactions	Reading schedule not specified Patients reported to the clinic if they observed a reaction after the final day 4 reading	After day 4	Initial testing: late reactions occurred to metals (mercury and nickel), neomycin, and textile dyes Repeat testing of 6 patients: 4 had pos reactions at earlier points (day 2 or 4) to PPD, basic red, disperse blue 106/124, and neomycin
Higgins and Collins, ³ 2013	British Society for Cutaneous Allergy standard series of allergens and additional allergens based on patient history	203	Days 2, 4, and 7	Day 7	26 Patients had delayed pos reactions on day 7; total 28 pos reactions to 21 allergens Late reactions to metals, disperse blue mix, fragrances, preservatives, colophony, and gentamicin sulfate
Hillen et al, ⁴ 2011	PPD at 3 concentrations in 3 patient groups: group 1 PPD 0.5% pet (range, 0.45%–0.5% pet) group 2 PPD 0.4% pet (range, 0.36%–0.44% pet) group 3 PPD 0.35% pet (range, 0.33%–0.35% pet)	1838 tested; data for 1666 were used in the analysis	Days 1–4 and days 2–4 Additional readings on days 7, 14, and 21 If patients unable to present for late readings, they returned to clinic only if they observed reactions	Day 7 or later	No late reactions to corticosteroids or PPD Newly pos late reactions in 8 patients (groups 1 and 2 only) 4/5 Retested patients had a pos reaction on days 2–3 Delayed reactions to PPD may be related to concentration and length of application Late reactions to PPD may represent active sensitization
Isaksson, ⁵ 2007	Case 1: institution's standard series, corticosteroid series, and a textile dye mix Case 2: institution's standard series and materials from the patient's workplace (a restaurant)	2	Days 3 and 7	After 7 days	Case 1: neg reaction on day 3, with pos reaction on day 7 to alclometasone-17,21-dipropionate 1.0% dimethyl sulfoxide Case 2: reaction to budesonide 0.01% pet on day 7 after an initial neg reaction on day 3
Madsen and Andersen, ¹⁶ 2013	TRUE Test patch-test allergens	9997 with eczema	Days 3–4 and days 6–7	Days 6–7	881/6509 Pos reactions (13.5%) were delayed pos reactions Late readings were most useful for neomycin sulfate, imidazolidinyl urea, diazolidinyl urea, lanolin, caine mix, hydrocortisone-17-butyrate, and budesonide >10% of pos reactions would have been missed without the additional reading

Malinauskiene et al, ⁶ 2010	Institution's baseline allergen series, included textile dye mix 6.6% and PPD	1	Days 3 and 7 for all allergens; days 10 and 14 for select allergens	Day 10 or later	Initial testing: reactions to Disperse Orange 1 (1.0% pet) on day 7, Disperse Yellow 3 (0.5% pet) on day 10, and PPD (0.94% pet) on day 14 (dyes applied on day 3 or 7) Subsequent testing (3 y later): late reaction to Disperse Orange 1 (1.0% acetone) on day 14; no reactions to Disperse Yellow 3 or PPD
Soria et al, ¹⁷ 2011	Conducted patch, prick, and intradermal tests with 5 corticosteroid preparations Additional patch tests were conducted with the same preparations diluted 0.1% in ethanol	19 patients with previously pos patch-test reactions to corticosteroids; 3 control patients	8 Hours; days 1, 2, 4, and 7	Between days 3 and 7	Patch-test removal on day 2 or 4, with readings between days 3 and 7, was most useful for detection of pos reactions to corticosteroids Late reactions on day 7 were seen in 6/19 patients to methylprednisolone sodium succinate/NaCl 30%, betamethasone disodium phosphate/NaCl 100%/NaCl 30%, hydrocortisone sodium succinate/NaCl 100%, methylprednisolone sodium succinate/NaCl 100%/NaCl 30%, betamethasone sodium phosphate/ethanol 0.1%, hydrocortisone acetate/ethanol 0.1%, budesonide, and budesonide/ethanol 0.002%/ethanol 0.01%
Thomas et al, ¹⁸ 2015	Institution's baseline 29-allergen series, bone cement component series, and a supplemental series that included neomycin sulfate	250 patients with cobalt-copper-molybdenum-based arthroplasties	Days 2, 3, and 6	Day 6	Delayed reactions occurred most frequently with gentamicin sulfate (17/25 late reactions) and nickel (II) sulfate (11/32 late reactions) Day 6 readings were useful for testing reactions to metals (nickel, cobalt, chromium) and bone cement components (especially gentamicin sulfate)

*Manufacturer information as provided by study authors: Pedilen (Otto Bock Scandinavia AB, Norrköping, Sweden), Lupranat (BASF AB, Göteborg, Sweden), and Desmodur (Bayer AB, Göteborg, Sweden). 4,4'-MDA, 4,4'-diaminodiphenylmethane; 4,4'-MDI, diphenylmethane diisocyanate; MDI, diphenylmethane diisocyanate; neg, negative; pet, petrolatum; pos, positive.

identified the preservatives imidazolidinyl urea, thimerosal, diazolidinyl urea, and methylchloroisothiazolinone/methylisothiazolinone as common causes of delayed positive reactions in their series. Higgins and Collins³ also observed late (day 7) positive reactions to preservatives, specifically methylchloroisothiazolinone/methylisothiazolinone, propyl gallate, and diazolidinyl urea Germall II. Of the 26 patients who had late positive reactions in their study, Ahlgren et al² observed a late reaction to dodecyl gallate in 1 patient.

Active Sensitization

Other series have investigated the possibility of active sensitization rather than contact allergy. Lucas Costa et al¹³ reported 2 patients with reactions at the site of metal allergen application and then positive reactions to beryllium with subsequent patch testing, which they suggested was attributable to active sensitization to beryllium. The focus of the study by Aalto-Korte et al¹¹ was patch-test sensitization. They reported that PPD was the most common allergen to cause sensitization with repeat testing. In their case report, Malinauskiene et al⁶ conducted repeat testing for active sensitization. Although they did not identify active sensitization upon repeat testing, they did identify a new late reaction to Disperse Orange 1.

The occurrence of active sensitization is an important area of study, but it requires patients to return for a second set of patch testing. Given the duration of our reading period and the logistics of bringing patients back for repeat patch testing, we did not repeat testing in patients with delayed positive reactions. Further studies investigating active sensitization are warranted.

Strengths and Limitations

Although a patch-test schedule that includes delayed readings can be onerous for patients, a large cohort of patients was compliant with late readings. Furthermore, we limited our analysis to only those allergens tested in at least 50 patients. As detailed previously,²⁰ all dermatologists (staff physicians, fellows, and residents) at our institution can perform patch testing under the supervision and advice of a 10-physician group specializing in contact dermatitis. This potentially could have led to variability in the interpretation of reactions.

In addition, for metals such as cobalt and gold, our institution uses multiple formulations (Table 1). The positive reactions on day 7 may be associated with the vehicle used, rather than the primary allergen itself. Studies addressing different formulations of patch-test allergens would further elucidate the relevance of late reactions.

CONCLUSIONS

A patch-test reading schedule that includes late readings (after day 7) is particularly useful for metals (gold, cobalt, beryllium, palladium), specific preservatives (dodecyl gallate, propolis), and the topical antibiotic neomycin. For other patient populations, a patch-test schedule that concludes with a day 5 reading will identify reactions to most allergens. In contrast to our previous study, delayed reactions to bacitracin were not detected. Late reactions to PPD and topical corticosteroids were not seen in this cohort, consistent with our previous study.

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