the Patch Tester

Contact Dermatitis | Haptens | Patch Testing

Edition #13
January 2023

THE EUROPEAN BASELINE EDITION

"The Patch Tester" is a quarterly e-magazine from Chemotechnique to the Patch Testers of the world.

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PURPOSE

The Patch Tester is an e-mag developed by Chemotechnique to serve as an information resource for all Patch Testers and other Dermatologists around the world; not just in Sweden, or Europe, or America, but wherever the English language can be read and understood. This thirteenth issue comprises forty-two pages with various different topics and features. Ultimately, we plan for The Patch Tester to become the forum for all of us to communicate and cooperate, in all directions.

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David Alsheimer-Niklasson & Steve Lee

The European Baseline Series and Recommended Additions 2023

By S Mark Wilkinson et al
In CONTACT DERMATITIS, November 2022, Accepted for publication.
See https://doi.org/10.1111/cod.14255

In 2017, the European Baseline Series (EBS) taskforce was formed as a working group of the European Society of Contact Dermatitis (ESCD).
A revision of the EBS was published for 2019. In that 2019 revised EBS, some changes were made from the previous edition.

Primin 0.01% (pet) was deleted due to infrequent positive patch test results and lack of clinical relevance.
Clioquinol 5% (pet) was deleted due to infrequent positive patch test results and lack of clinical relevance.
Propolis 10% in pet was added.
2- hydroxyethyl methacrylate (2-HEMA) 2% in pet was also added.
Caine mix III 10% in pet was to be added to replace **benzocaine 5% in pet.**, given the increased sensitivity of the mix in screening for contact sensitisation to local anaesthetics. It was felt that some of the haptens proposed as potential further additions did not fully meet the criteria for inclusion in the EBS, but that whilst further information was gathered to confirm or refute their importance, testers should consider the potential value of being testing to them in their specific population. These

haptens were listed as recommended additions to the EBS.

The intention of the group was to create a biennial update of the EBS to coincide with the biennial congress of the ESCD to which all members of the ESCD would have the opportunity to contribute. Results of the European Surveillance System of Contact Allergy (ESSCA) and an audit of the proposed changes once implemented confirm that the existing haptens within the EBS occur with a frequency to merit their continued inclusion. However, the continued inclusion of methyldibromoglutaronitrile (MDBGN) has been questioned due to a lack of current clinical relevance. However, it has been pointed out that relying on MDBGN results obtained with the TRUE Test might severely under-estimate sensitisation prevalence owing to under-dosing.

2019 Additions to the EBS

Of the 2019 additions, all occurred with a frequency to merit continued inclusion.
These were specifically:

• **2-hydroxyethyl methacrylate (2-HEMA) 2% pet.**: It was noted that the European Union had recognised the frequency of problems caused by home use of nail acrylates and had limited the use of 2-hydroxyethyl methacrylate (HEMA) and 11,14-Dioxa-2,9-diazaheptadec-16-enoic Acid, 4,4,6,16-tetramethyl-10,15-dioxo, 2-[(2-methyl-1-oxo-2-propenyl)oxy]ethyl ester (Di-HEMA Trimethylhexyl Dicarbamate or Di-HEMA TMHDC) to professional use only in November 2020.

• **Caine mix III 10% pet.:** Whilst the mix was more sensitive than testing to benzocaine 5% alone as a screen in detecting contact allergy to topical local anaesthetic, where allergy is suspected. it is important to note that due to false patch negative test reactions, it is still important to test to the individual constituents. This is similar to the situation with fragrance allergy and the fragrance mix (FM) where the mix is an adequate screen but fails to detect all allergic reactions. Frequently a mix is a compromise to increase the scope of allergies covered by the EBS, but to reduce the risk of irritation individual constituents of FM I may be tested at a lower concentration than they would be when tested alone and was the strategy when developing FM II.

2022 changes to the EBS

• **Formaldehyde releasing preservatives:**
Formaldehyde 2% aq. was effectively included in the EBS from 2014, with a doubling of the rate of detection of formaldehyde allergy.

The formaldehyde-releasing preservatives imidazolidinyl urea 2% pet., **diazolidinyl urea 2% pet.** and **2-bromo-2-nitropropane- 1,3-diol 0.5% pet.** was added in 2019 to the extended baseline series. It was however then unclear to what extent testing with above formaldehyde releasers yields additional relevant information above screening with formaldehyde 2% aq. and quaternium-15 1% pet. When reviewing the results from ESSCA, it was demonstrated that formaldehyde 2% aq. is not a good predictor of allergy to the formaldehyde releasers. However none of the individual formaldehyde releasers elicited positive patch test reactions with a frequency sufficient to warrant inclusion in the EBS.
Despite this, it was t concluded that the formaldehyde releasers 2-bromo-2-nitropropane-1,3-diol 0.5% pet. and diazolidinyl urea 2% pet. should remain as recommended additions to the EBS as

they occurred with a frequency at the threshold for inclusion. It was decided to remove **Quaternium 15 1% pet**. from the EBS as it co-reacts most frequently with formaldehyde 2% aq. not yielding sufficient additional positive reactions to warrant inclusion. Further, Quaternium 15 together with formaldehyde was restricted from use in cosmetic products by the European Union in 2019 and it would be anticipated that contact allergy from this source would further decline. It should be kept in mind that in occupational materials and cosmetic products acquired outside the European Union quaternium-15 may still be present and directed testing may be required when indicated.

• **Sodium metabisulfite 1% pet.** demonstrated frequent positive reactions across a wide geographic range and it was decided to include this allergen within the EBS. Whilst relevance to this preservative was not always clear, the group agreed that it was probable that exposure to this allergen was wider than currently appreciated and that with time relevant exposures would become more clearly established. This is a particular issue in products where, unlike with cosmetics, pharmaceuticals and food, there is no ingredient labelling. For example, the presence of sulphites has been suggested in synthetic and natural rubber gloves, catheter systems and leather footwear.

• **Methylisothiazolinone and benzisothiazolinone (BIT) 0.1% pet**. and **octylisothiazolinone (OIT) 0.1% pet**. were included as recommended additions to the EBS in 2019, following on from the epidemic of contact allergy to these substances. Review of testing demonstrated that BIT allergy occurred with an increasing frequency thereby meriting inclusion in the EBS, although clinical relevance was not always clear.

• **Decyl glucoside 5% pet.** and **lauryl glucoside 3% pet.** have both been recognised as common cosmetic haptens within North America. Audit of testing in Europe demonstrated allergy to decyl glucoside to be the more frequent, thereby meriting inclusion within the EBS. In view of frequent cross reactions with lauryl glucoside, the additional yield from testing lauryl glucoside in the EBS was insufficient to warrant inclusion. However, as additional glucoside allergy is detected by individual testing it is recommended that other glucosides be tested in a cosmetic series when indicated.

• **Sorbitan sesquioleate 20% pet.** and **sorbitan mono-oleate 5%.** It has been suggested as an addition to the EBS both on the basis of the frequency of its occurrence and because it is an ingredient of some hapten preparations used
for testing leading to inaccurate diagnosis and inappropriate advice being given e.g., FM I 8% pet and Myroxylon pereirae resin 25% pet. Although some countries have found a high prevalence of sensitivity to this hapten, other members of the EBS taskforce commented that there was large geographic variation. It was agreed to add sorbitan sesquioleate 20% pet. and its constituent sorbitan mono-oleate 5% pet. as recommended additions to the EBS until further data was acquired.

Editor's Note: In the next issue of The Patch Tester, #14 due out in March 2023, we will have two editorial articles on the new European Baseline Series 2023:

1. *Showing the availability of the various Chemotechnique haptens corresponding to the new European Baseline Series 2023*

2. *Comparing the EBS 2023 with the TRUE Test® patch test system.*

6 What's New in Patch Testing?

The 2023 EBS Series (S-1000):
(the 2023 additions in blue)

Pos	Art. no	Hapten
1	P-014A	Potassium dichromate
2	P-006	p-PHENYLENEDIAMINE (PPD)
3	Mx-01	Thiuram mix
4	N-001	Neomycin sulfate
5	C-017A	Cobalt(II)chlorid e hexahydrate
6	Mx-19	Caine mix III
7	N-002A	Nickel(II)sulfate hexahydrate
8	H-010	2-Hydroxyethyl methacrylate
9	C-020	COLOPHONIUM
10	Mx-03C	Paraben mix
11	I-004	IPPD
12	W-001	LANOLIN ALCOHOL
13	Mx-05A	Mercapto mix
14	E-002	Epoxy resin, Bisphenol A
15	B-001	Peru balsam
16	B-024	PTBP
17	M-003A	MBT
18	F-002B	FORMALDEHYDE
19	Mx-07	Fragrance mix I
20	Mx-18	Sesquiterpene lactone mix
21	**S-011**	**Sodium metabisulfite**
22	P-022	Propolis
23	C-009B	MI/MCI
24	B-033B	Budesonide
25	T-031B	Tixocortol-21-pivalate
26	D-049E	MDBGN
27	Mx-25	Fragrance mix II
28	L-003	Lyral
29	M-035B	METHYLISOTHIAZOLINONE
30	**B-003B**	**Benzisothiazolinone**
31	Mx-30	Textile dye mix
32	**D-065**	**Decyl glucoside**

Removed haptens:
QUATERNIUM-15 (C-007A)

The 2023 EBS Series with recommended additions (ECB-1000) *(the 2023 additions in blue)*

Pos	Art. no	Hapten
1	P-014A	Potassium dichromate
2	P-006	p-PHENYLENEDIAMINE (PPD)
3	Mx-01	Thiuram mix
4	N-001	Neomycin sulfate
5	C-017A	Cobalt(II)chloride hexahydrate
6	Mx-19	Caine mix III
7	N-002A	Nickel(II)sulfate hexahydrate
8	H-010	2-Hydroxyethyl methacrylate
9	C-020	COLOPHONIUM
10	Mx-03C	Paraben mix
11	I-004	IPPD
12	W-001	LANOLIN ALCOHOL
13	Mx-05A	Mercapto mix
14	E-002	Epoxy resin, Bisphenol A
15	B-001	Peru balsam
16	B-024	PTBP
17	M-003A	MBT
18	F-002B	FORMALDEHYDE
19	Mx-07	Fragrance mix I
20	Mx-18	Sesquiterpene lactone mix
21	**S-011**	**Sodium metabisulfite**
22	P-022	Propolis
23	C-009B	MI/MCI
24	B-033B	Budesonide
25	T-031B	Tixocortol-21-pivalate
26	D-049E	MDBGN
27	Mx-25	Fragrance mix II
28	L-003	Lyral
29	M-035B	METHYLISOTHIAZOLINONE
30	**B-003B**	**Benzisothiazolinone**
31	Mx-30	Textile dye mix
32	**D-065**	**Decyl glucoside**
33	B-015B	2-Bromo-2-nitropropane-1,3-diol
34	D-044A	Diazolidinyl urea
35	O-004	2-n-Octyl-4-isothiazolin-3-one
36	Mx-29B	Compositae mix II
37	H-031A	Linalool hydroperoxide
38	H-031B	Linalool hydroperoxide
39	H-032A	Limonene hydroperoxide
40	H-032B	Limonene hydroperoxide
41	S-005	Sorbitan sesquioleate
42	S-004	Sorbitan monooleate

Removed haptens:
QUATERNIUM-15 (C-007A)
IMIDAZOLIDINYL UREA (I-001A)
LAURYL POLYGLUCOSE (L-004)

Dear Reader, if you have any particular article or book or website that you would like to have reviewed in a future issue of The Patch Tester, then please contact the Editor here.


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Orders being picked by the order department

The Ordering Department

The ordering department, led by department head Jessica Mückenheim, plays a vital role in ensuring that patch test products are properly packed and shipped to customers in a timely manner.

The team works closely with the manufacturing department to ensure that the products are of the highest quality and that the correct products are delivered to customers. They also maintain detailed records of all products shipped, including tracking information, to ensure that customers can easily track their orders.

Under Jessica's leadership, a culture of continuous improvement within the department is encouraged, and team members are regularly trained on new techniques and technologies to improve their efficiency and the quality of their work.

The department is also focused on reducing their environmental impact with efforts to implement more sustainable packing materials and shipping methods.

Thanks to the hard work and dedication of the team, customers can be confident that their orders will be handled with care and shipped promptly, and that the products they receive will be of the highest quality. The department has also helped in reducing the company's carbon footprint, which is an important aspect for many customers today.

Overall, the ordering department plays a key role in creating a positive customer experience and ensures that Chemotechnique remain the Trusted Name in Patch Testing.

Cobalt

Patch Testing with Cobalt in Children & Adolescents: NACDG Experience 2001-2018

By Jonathan Silverberg, et al
In CONTACT DERMATITIS, Volume 87, Issue 4, October 2022, pp 420-429.
See https://doi.org/10.1111/cod.14185

This original article serves as an update on the importance of Cobalt as a contact allergen to children and adolescents. Although based on experience in America, the results and conclusions are equally applicable to the European and indeed the global situation, due to the global presence of cobalt in so many common items.

Summary
In summary, cobalt chloride is a metal salt derived from the cobalt metal that is found ubiquitously in modern life and products. Cobalt is often a cause of allergic contact dermatitis (ACD) in children. It is one of the top three most common allergens to cause ACD in children in North America. A systematic review of 34 international studies of patch testing in children and adolescents found cobalt to be one of the most common allergens in children with the prevalence ranging from 9.5% to 17.8% around the world. The wide range in prevalence of cobalt allergy in children may be explained by variation in exposures in different countries. Reported sources of cobalt include jewellery, belts, cosmetics, children's toys, dental and other implanted devices, and rarely leather products.

Purpose
The purpose of the study was to assess trends in positive and clinically relevant patch test reactions to cobalt in children and associated patient characteristics, common sources and body sites affected.

This is the first large-scale study that identifies the characteristics and sources of cobalt allergy in children.

The study is based on a retrospective analysis of 1919 children (<18 years) patch tested to cobalt by the North American Contact Dermatitis Group between 2001 and 2018.

Of the 1919 children patch tested, 228 (11.9%) and 127 (6.6%) had a positive/allergic or currently relevant patch test reaction to cobalt, respectively.

ACD is often underdiagnosed in children due to infrequent patch testing and misdiagnosis of the eczematous eruptions.

Hapten of the Quarter

It is recommended that any child with persistent eczema get patch tested, regardless of the pattern of dermatitis. In fact, patch testing and identification of relevant allergens in those with suspected ACD was shown to improve quality of life.

Study population
Overall, 1919 children (<18 years) were patch tested with cobalt between 2001 and 2018.
Among children who were patch tested, 36.2% were male, 79.8% white and only 6.9% employed, with an average age of 12.5 ± 3.8 years.

Symptoms
Atopic disease was common (64.0%) with 51.8% having history of atopic dermatitis, 22.8% having asthma and 32.5% having hay fever.

Body Sites
Body sites commonly involved included:

- scattered generalised (30.0%)
- hands (14.9%)
- legs (14.7%)
- face (20.3%)
- trunk (10.1%)
- not specified.

Affected body site(s) varied by cobalt source among patients with currently relevant reactions, especially for less common sources.

Prevalence + Positivity Rates
Children in this study were referred for patch testing with suspicion for ACD, and therefore prevalence estimates are not representative of the general paediatric population.

Several studies assessed the prevalence of cobalt allergy in children and adolescents, with prevalence varying from 4% to 17%. A systematic review of 34 international patch testing studies found cobalt to be one of the most common allergens in children (9.5%– 17.8%). Some studies examined cohorts that included both adults and children, and prevalence varied from 6.7% to 14%. In a meta-analysis of 24 European and North American studies, the prevalence of cobalt allergy was 2.7% in children and adults. Interestingly, this meta-analysis found no significant difference in the prevalence of contact allergy between adults and in children.

In this study, irritant morphology was not uniformly coded, and only about 50% of those children had a final interpretation of irritant reaction, while 10% were interpreted to be allergic, 15% to be unknown and 25% to be negative reactions, suggesting that these irritant reactions may be difficult to interpret, and false-positive or false-negative reactions are likely.

Previous North American studies found that children have higher rates of allergic and relevant patch test reactions to cobalt than adults. However, there is limited information on the characteristics and sources of cobalt allergy in children.

Cobalt-positive Reactions
Of the 1919 children who were patch tested, 228 (11.9%) had a positive allergic reaction and 127 (6.6%) had a currently relevant reaction to cobalt on patch testing; 275 (14.3%) reacted to cobalt in some form.

+ reaction	n = 100	36.3%
++ reaction	n = 67	24.4%
+++ reaction	n = 56	20.4%
+/ reaction	n = 52	18.9%
Irritant reaction	n = 37	11.9%
Sum	n = 312	

Of the 52 (2.7%) patients who had macular erythema/irritant morphology, 27 (51.9%) had a final interpretation of irritant, 5 (9.6%) had allergic, 8 (15.4%) had unknown reactions and 12 (23.1%) were determined to be negative reactions.

Allergic reactions to cobalt peaked at 14–15 years of age, however they remained fairly stable throughout childhood, fluctuating between 12% and 14%. There was more variability in current relevance of cobalt reactions, with a peak at 6–7 years. The strength of patch test reactions also varied considerably throughout childhood.

Associations with allergic and other clinically relevant reactions to Cobalt
In this study, no significant associations were found between positive or currently relevant allergic reactions to cobalt with sex, occupational relevance, atopic history (eczema, asthma, hay fever), race or employment. This is in contrast to other studies which found that children with cobalt allergy are more likely to be female and have a history of atopic dermatitis or atopy. A Polish study of 9320 children found that every second child with atopic eczema has a positive patch test result, and every third child ultimately was diagnosed with ACD.

Clinical relevance
Of 127 (6.6%) children who had a currently relevant reaction, these were categorised as follows:

Possible Relevance	n = 95	74.8%
Probable Relevance	n = 26	20.5%
Definite relevance	n = 6	4.7%
Past relevance	n = 39	2.0%
Unknown Relevance	n = 67	3.5%.

Of the 228 children determined to have cobalt allergy, these were categorised as follows:

Currently Relevant	n = 125	54.8%
Past Relevance	n = 38	16.7%
Unknown Relevance	n = 62	27.2%
Not Applicable	n = 3	1.3%.

Sites of Dermatitis
Among children with an allergic reaction to cobalt, the most common primary body sites were scattered generalised (30.0%), face (10.6%) and trunk (10.1%). In a previous study of cobalt allergy in adults, hand dermatitis was more common. This is likely because adults more often encounter cobalt in occupational settings in sources like tools, cement, concrete, mortar and other building and construction materials. The authors of the study found that children more often encounter cobalt in belts and clothing, which both are more likely to come in contact with patient's trunk or in a generalized distribution. The sites of dermatitis affected in patients with cobalt relevant reactions correlate with sources of cobalt.

Children with versus without cobalt allergic reactions were more likely to have a primary dermatitis site of trunk, and ears, and less likely to have a primary site of face.

Similarly, children with currently relevant cobalt reactions were more likely to have a primary site of trunk, and ears, but less likely to have a primary site of foot.

Sources of Cobalt
Among patients with cobalt allergic reactions, the sources were defined as follows:

- Clothing, wearing apparel, protective equipment, textiles (n = 117 [89.3%])
- Building and construction materials, tools, equipment, supplies (n = 4 [3.1%])
- Jewellery (58.8%)
- Clothing (10.7%)
- Belts (7.6%)
- Watches (3.8%)
- Shoes (0.8%)
- Dental prostheses (0.8%)
- Food products (0.8%).

Among children with currently relevant cobalt allergic reactions, affected body sites were similar for the most common sources of cobalt. Jewellery was the most common source for most primary body sites, except the face, leg, other body sites, clothing exposed and only under clothing.

Belts, shirts, pants, blouses, dresses, skirts, surgical scrubs and smocks were among the most common sources for dermatitis affecting scattered generalised, trunk and arms.

Hand dermatitis had the most variable sources, being commonly caused by building materials, coatings and adhesives, recreational and athletic equipment, textiles and fabrics (14.3% each).

Lip dermatitis was commonly caused by dental products, essential oils, furniture and writing/drawing supplies (16.7% each).

Foot dermatitis was caused by footwear (25.0%).

Anal/genital reactions were caused by medications (33.3%).

Jewellery was the most common source for scattered generalised, trunk, arms, ears and eyelids and is a well-established source of cobalt in both children and adults. Cobalt in jewellery can cause

scattered generalised reactions likely due to progression from a localised reaction, which cobalt is known to do. Interestingly, jewellery that contains cobalt tends to be darker silver in colour, which may aid patients with cobalt allergy when purchasing jewellery.

Although cases of cobalt allergy from belts were previously reported, it is much less common than nickel allergy from belts. In contrast to nickel, cobalt release was more frequently detected in branded belts than non-branded belts, likely because of the higher cost of cobalt compared to nickel. Similar to jewellery, dark metallic belts more commonly release cobalt than silver, copper or gold coloured belts.

Clothing is also an important source of cobalt allergy. Metallic accessories on clothing items, for example, buttons and zippers, often release cobalt and may be a relevant source in both children and adults.

Cobalt was recently shown to be associated with dermatitis due to leather products, particularly in shoes and furniture. In our study, footwear was a rare cause of cobalt allergy affecting only one patient on the feet, while furniture affected two children in a scattered generalised distribution.

The study authors found that dental materials or prostheses were a source of cobalt in two patients. These are established sources of cobalt exposure; however, it seems likely that most cobalt allergic patients with such implants do not develop ACD.

Adults with cobalt allergy often react to cobalt in cosmetics and hair care products. While these were not sources of cobalt allergy for children in this study, cobalt was previously identified in children's toy makeup. Children's toys as a source of cobalt were recently discussed, though cobalt is generally not found in toys, and is less common than nickel. While the study authors did not specifically identify cobalt in children's toys, these reactions may have been coded in other broad categories, for example, "miscellaneous consumer items" or "not elsewhere classified".

Crayons were also reported as a source of cobalt. In this study, writing, drawing supplies and art supplies was associated with lip dermatitis in one patient.

Building materials were a source of cobalt in 14.7% of children with hand dermatitis, likely from exposure to metal tools and fixtures that children may be exposed to at home. Other reported sources include paints, animal feeds and glass, all of which were uncommon in this study.

The source of cobalt was unknown for most body sites, suggesting that more information is needed on the potential exposures of cobalt for children.

Patch Test for Cobalt

Over the study period, a switch in cobalt test formulations in 2009 was made from cobalt chloride 1% in petrolatum (pet.), an anhydrous sky-blue metal salt, to cobalt chloride hexahydrate 1.0% pet., a hydrated bright pink metal salt. When comparing the two formulations, cobalt chloride led to significantly higher rates of allergic reactions than cobalt chloride hexahydrate. This may be due to higher false-positive "poral" reactions with the anhydrous formulation that was previously used. "Poral" reactions have a speckled appearance, without oedema or confluent erythema, and are considered irritant reactions rather than allergic reactions. Testing with lower concentrations of cobalt is not recommended as false-negative reactions tend to increase at concentrations less than

1%, thus “poral” reactions must be kept in mind when using cobalt chloride 1% or higher.

When comparing the two different formulations of cobalt used by the NACDG group (2001–2008: cobalt chloride 1.0% pet., 2009– 2019: cobalt chloride hexahydrate 1.0% pet.), cobalt chloride had significantly higher rates of allergic reactions (n = 109/736 [14.8%]) than cobalt chloride hexahydrate (n = 119/1183 [10.1%].

Cobalt Spot Test
Thyssen and colleagues developed a spot test for detecting cobalt in items using disodium-1-nitroso-2-naphthol-3,6-disulphonate, similar to the dimethylglyoxime test for nickel. However, the spot test gives a yellow-orange colour in the presence of cobalt rather than the pink colour observed in the Nickel Spot Test. This test can be helpful for clinicians to establish the clinical relevance of cobalt reaction, and for patients to avoid cobalt in the real world when the presence of cobalt in a product is under question.

Co-sensitisation to other Metals
Cobalt sensitivity commonly co-occurs with sensitivity to other metals, for example, nickel and chromium, likely as a result of concomitant exposure and sensitivity rather than cross-reactivity. Further analysis is needed to further characterise the demographics, sites, cobalt sources, and patch reactions/relevance of children with multiple metal allergies versus those with a single metal allergy. Some alloys of cobalt also contain nickel or chromium, thereby making it difficult to ascertain whether allergic reactions are specific to cobalt without assessing patch test reactions to other metals.

Patch Testing for Cutaneous Adverse Drug Reactions in Paediatric Population

By Joni Costa Carvalho, et al
In CONTACT DERMATITIS, Volume 87, Issue 4, October 2022, pp 373-376.
See https://doi.org/10.1111/cod.14167

Non-immediate cutaneous adverse drug reactions (CADRs) are mostly clinical manifestations of a Type IV hypersensitivity reaction. In children, diagnosing CADRs is a common challenge for physicians, as childhood rashes are more often due to viral infections but frequently mimic CADRs. A proper diagnosis and identification of the culprit drug avoids misdiagnosis, therefore, preventing unnecessary drug avoidance or replacement, and guidance for potential alternatives reducing morbidity from CADRs. Patch tests (PT) are considered useful for diagnosing non-immediate CADRs; however, few paediatric studies have been published. This may be related to the lower incidence of CADRs in children, the lack of PT standardisation especially for severe cutaneous adverse reactions (SCARs), and controversies on PT safety, particularly in this population.

The retrospective study by Carvalho et al over 11 years to 2021 at Coimbra University Hospital aimed to evaluate the sensitivity and safety of the Patch Test for the diagnosis of CADRs in the paediatric population.

Over the 11 years, just 22 cases presented with presumed CADR, with 11 males and 11 females. Median age was 13.5 years.

The suspected diagnoses were:

- Macro Papular Exanthem in 17 cases (77.2%)
- DRESS in 3 cases (13.6%)
- Stevens-Johnson Syndrome in 1 case (4.5%)
- Toxic Epidermal Necrolysis in 1 case (4.5%).

The identified causes of the drug reactions were:

- Antibiotics (70%)
- Beta Lactam antibiotics (75% of the 70%)
- NSAIDs + Alpha-amylase suspected in 27% of cases
- Vancomycin (12%)
- Flucloxacillin (12%)
- Carbamazepine (40%)

Cross-reactivity was observed in two patients, flucloxacillin – dicloxacillin and carbamazepine – oxcarbamazepine

A secondary diagnosis of Allergic Contact Dermatitis was confirmed in 2 cases, one from tioconazole and one from methylisothiazolinone.

Although the number of patients in the study was small, their clinical characteristics indicated that children with severe or highly suspected mild CADRs were the ones tendentially referred for PT, as has been found in other studies.

PT positivity rate was similar to the literature, indicating an overall low sensitivity and a widely variable sensitivity depending on the clinical presentation and the culprit drugs.

Previous studies have shown that exanthema from other causes, such as infections or complex interactions between drugs and viruses, are one of the main reasons for the apparent low sensitivity of the patch test to identify the causative drugs of Macro-Papular Exanthema.

For Serious Cutaneous Drug Reactions (SCARs), the sensitivity of the patch test is related mainly to the involved drugs (higher with anticonvulsants) and because the probability of a positive PT increases with the severity of the CADRs, as has been shown in several previous studies.

In this paediatric population, as in adults, the patch test was safe.

Also, for paediatric cases, the patch tests confirmed the culprit drug in a significant percentage of patients, and thereby suggested potentially safer alternatives in SCARs, particularly to anticonvulsants.

Due to the relatively low sensitivity of PT in suspected MPE to beta-lactams, patch tests do not fully replace drug provocation tests (DPTs), which are considered the gold standard diagnostic tool in these cases.

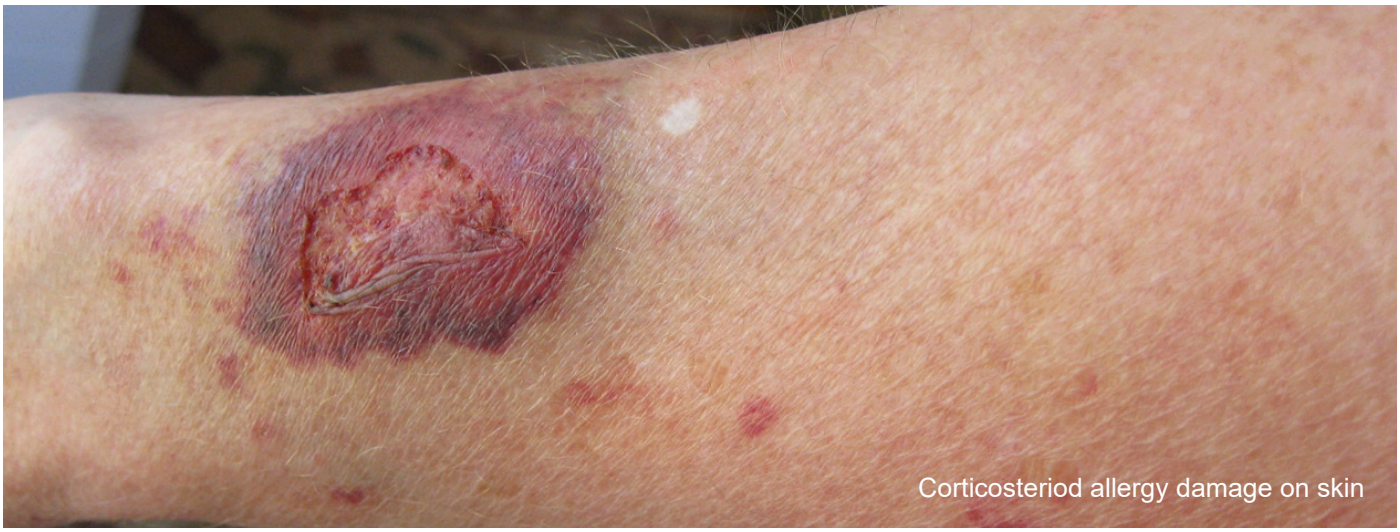
However, intradermal tests also have low sensitivity, and together with the difficulty of performing such painful tests in children, several studies recommend a direct DPT in ‘benign CADRs’. For drugs other than beta-lactams, there is some controversy on a direct DPT. Apart from being time-consuming when more than one culprit is suspected, DPT are contraindicated in SCARs. Therefore, we can recommend PT as a safe first step in the study of non-immediate CADR, particularly from drugs other than beta-lactams.

Despite the data presented here and in previous studies, more studies are needed to establish PT sensitivity in the paediatric population.

As always, for full information, please read the original article in CONTACT DERMATITIS.

The Benefit of late Patch Test Readings in Corticosteroid Allergy

By Sebastian Vigand Svendsen, et al
In CONTACT DERMATITIS, Volume 87, Issue 4, October 2022, pp 466-468.
https://doi.org/10.1111/cod.14197



Corticosteriod allergy damage on skin

Allergic contact dermatitis (ACD) to corticosteroids remains a diagnostic and therapeutic challenge for clinicians. Patch testing is the golden diagnostic standard, which is recommended to be read twice, on day (D) 2, D3, or D4 and D7, although some practitioners skip the late reading.

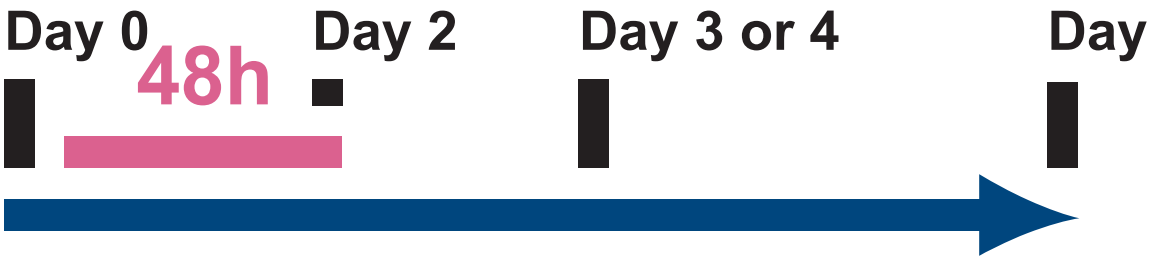
Previous studies have suggested late reading of corticosteroids, but conclusive data has been lacking. This retrospective study was therefore devised by the authors to investigate the benefit of Day 7 patch test readings for corticosteroid haptens.

The authors based in Odense Denmark used TRUE Test and/or individual corticosteroid haptens in either petrolatum or ethanol.

Patch tests were performed according to ESCD recommendations, with readings on D3/D4 and D7. Reactions designated as either +, ++ or +++ were positives. Follicular (F) and doubtful reactions (?+) were registered and classified as negatives.

A total of 10,746 patients were patch tested with corticosteroid allergens.

- A total of 505 positive reactions were found, in 201 patients (1.9%).
- In total, 53.7% (271/505) were positive reactions on D3/4 and D7.



- The authors found 28.1% delayed positive patch test reactions (142/505) of which 26.1% (37) were evaluated doubtful ?+ at D3/4.
- The delayed positives showed primarily weak positive (+) reactions (72.5%).
- In total, 18.2% (92/505) showed early positive reactions.
- A total of 28.1% of positive corticosteroids contact sensitisations would have been missed if only an early reading was performed.
- About 18.2% of sensitised were only found at D3/4 readings while 53.7% were found positive at both early and late readings.

Previous data on late reading of corticosteroid patch test are conflicting. In line with our results one study found 28.4% of corticosteroid-sensitised were new D7 positives; also in concordance with previous studies. However, very low number or even no new delayed positive reactions to corticosteroids have been reported from other clinics. These conflicting results can possibly be explained by the fact that corticosteroids possess dual effects caused by their allergenic and intrinsic immunological properties.

The diagnostic patch test reading is challenged by non-allergic erythema due to locally induced vasoconstriction causing blanching and secondary vasodilatation as a steroid effect, as well as the morphological “edge-effect” due to central relatively high concentration of corticosteroids inducing predominantly anti-inflammatory effect and peripheral allergic cutaneous manifestation. In addition, variation in patch test concentrations, materials, and diagnostic reading techniques might also explain the conflicting results.

The authors conclude that their study shows a 2.7% positivity rate in consecutively tested patients and that over a quarter of positive cases would be missed if Day 7 readings were not performed. Their results thereby emphasise the importance of late patch test readings on Day 7 in order to diagnose ACD to corticosteroids.

Patch Test results to extracts of Synthetic Garments in Textile Dye-positive Patients

By Kotryna Linauskiene, et al
In CONTACT DERMATITIS, Volume 87, Issue 4, October 2022, pp 325-330.
See https://doi.org/10.1111/cod.14182

Disperse dyes (DDs) are used for colouring synthetic textile materials based on fibres such as polyester, acrylic, acetate and polyamide. Eight DDs are included in a textile dye mix (TDM) 6.6% petrolatum (pet.) in the European Baseline Series. in the Swedish, European and International Contact Dermatitis Research Group Baseline Series since 2015, 2016 and 2019, respectively. The eight dyes are:

1. Disperse Blue 35
2. Disperse Blue 106
3. Disperse Blue 124
4. Disperse Yellow 3
5. Disperse Orange 1
6. Disperse Orange 3
7. Disperse Red 1
8. Disperse Red 17.

Within the Textile Disperse Mix, 6.6% pet., the DB 106 and DB 124 are tested at 0.3% each, whilst the other six DDs are tested at 1.0% each.

In the study, the authors collected textiles from 13 countries in Europe, USA and Asia for analysis.

Among 121 garments analysed, the authors found only four of the eight DDs, in three different garments. The conclusion one could draw was that the DDs that were patch-tested are not very widely used in garments anymore, but that you still can find them in some items, even in those items manufactured in Europe. Therefore, the authors decided to create their own patch test reagents based upon the material of the garments that they had collected and analysed.

From these textiles the authors created 24 patch test haptens, which were used alongside the TDM 6.6% in petrolatum supplied by Chemotechnique Diagnostics. Finn Chambers were used as the patch test chambers. The home-made solutions derived from textiles, were difficult to create and differences existed in concentration and purity, though every effort was made by the investigators to try to achieve a 5% concentration in petrolatum.

Patch testing was done according to the ESCD and ICDRG guidelines.

Clinically, DDs are the most prevalent causes of textile-related allergic contact dermatitis.

In previous studies where patch testing to TDM 6.6% pet had been performed, contact allergy frequency rates of 3.7% has been seen in a European/US study and 2.5% in a Swedish study, with overall clinical relevance of 31% and 37%, respectively. In the author's own clinic in Malmö Sweden, the contact allergy rate to TDM 6.6% pet. ranged from 1.7% to 3.5% (average 2.7%) between 2014 and 2019 with some variation but no trend in all their patch-tested dermatitis patients.

In this study, the authors found 73 TDM 6.6%-positive patients, patch tested between 2012 and 2017, who were invited to participate in the study. Just ten patients agreed to participate.

Of those, two patients did not react to TDM 6.6%:
1. One had a 3+ TDM 6.6% reaction in 2012 which was clinically relevant, since he reacted to a black belt made from leather. He had UV therapy several weeks before the present study and only informed the authors during patch test readings, when all 25 patch tests were negative.
2. The second individual, a woman, had a 1+ TDM 6.6% positive reaction only on D7 in 2012 and was negative on D3.

Of the 10 individuals, 8 reacted with a positive test reaction to TDM 6.6% pet. and 9 to 2 or more textile extracts.

A total of 20/24 extracts gave a positive reaction. One individual was positive to 19 extracts, another to 14 extracts, 3 to 5 extracts, 1 to 4 extracts, 1 to 3 extracts, and 2 to 2 extracts. Patients mostly

reacted to six textile extracts (three from items labelled ‘Made in China’, one from a garment labelled ‘Made in Spain’, one from an item labelled ‘Made in Bangladesh’ and one from a garment purchased in South Africa with no labelling information of its origin. All controls were negative to the tested extracts.

It has been shown in previous investigations that the eight DDs present in TDM 6.6% pet. also contain allergenic substances other than the actual dyes, and this has been shown by patch testing with thin-layer chromatograms. The presence of impurities in the TDM 6.6% has not been verified. The impurities are probably by-products from the synthesis of the dye molecules, excess raw-materials or otherwise related substances present in minute amounts compared to the actual dye molecule. An additional confounding factor is that the patch test suppliers could buy their dye test substances from different chemical companies, which possibly contain different impurities.

it has been shown that patch testing with the same substance on several occasions or multiple testing on several locations on the back will give varying results, sometimes positive and sometimes negative. This is especially seen with weak allergic test reactions.

The co-occurrence of multiple reactions to several extracts, even in the same patient, could trigger the hypothesis that there could be one (or more) mutually present substances/sensitisers in the extracts.

In conclusion, the authors state that their results from the present study prove that TDM-positive patients react to synthetic textile extracts that do not contain the pure DDs that are present in TDM 6.6% but to other dye substances, which we still do not know which they are. So the very important question is what type of dyes are being used nowadays, and if patch testing with TMD 6.6% is still relevant in light of the result the authors obtained.
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Today many DDs are still considered to be the most important haptens in textile dermatitis, but the uncertainty about their current use in textiles remains. Nevertheless, several previous studies have shown a good correlation between positive reactions to TDM 6.6% and a clinically relevant dermatitis in approximately a third of TDM-positive patients.

For full information, the reader is recommended to read the original article in CONTACT DERMATITIS.

A Closer Look at ACD caused by Topical Ophthalmic Medications

By Pedro Botelho Alves, et al
In CONTACT DERMATITIS, Volume 87, Issue 4, October 2022, pp 331-335.
https://doi.org/10.1111/cod.14174

Allergic contact dermatitis caused by topical ophthalmic medications (OftACD) is frequently difficult to confirm with patch testing and, therefore, it is considered uncommon. A recent cohort study in Belgium estimated an overall prevalence of 0.7% among more than 16 000 patients evaluated for contact allergy. Probably due to the difficulty of identifying the culprit, OftACD is likely underreported although it may cause significant impairment of quality of life.

The authors of the study collected retrospective data from a cohort of 65 patients with suspected OftACD out of a total of 4,891 patients who had been patch tested in their Dermatology Clinic in Coimbra Portugal over 16 years to 2021. The patch tests were done according to ESCD guidelines. All patients were patch tested with the European Baseline Series and an additional series of topical medications and excipients (supplied by Chemotechnique Diagnostics), and in selected cases with betaxolol chloridrate and timolol maleate kindly supplied by the pharmaceutical industry and prepared in the local pharmacy at 5% pet. Also, ophthalmic medications frequently used by the department of ophthalmology, as well as patient's own products were also patch tested 'as is' in most patients.

Many different classes of topical drugs are used for treating eye diseases – antibiotics for bacterial conjunctivitis or as perioperative prophylaxis, corticosteroids for inflammatory eye diseases (ex: anterior uveitis); antiseptics such as iodine povidone regularly used intraoperatively; and a wide range of anti-glaucoma drugs (beta-blockers, prostaglandin analogues, carbon anhydrase inhibitors). Additionally, preservatives have an important role in the formulation of these medications. However, single use preparations without preservatives have recently been recommended for chronic treatments in order to reduce the potential tissue damaging effect of these chemicals.
.
OftACD mainly presents with eyelid eczema, but it may include periorbital erythema, oedema or vesicles, sometimes involving also the malar area. Since eyelid dermatitis can be caused by other skin conditions (ex: atopic dermatitis, seborrheic dermatitis, irritant contact dermatitis, rosacea), patch testing is a valuable tool to establish a differential diagnosis and to identify the culprit allergen. Eyelids were the most commonly affected area (n = 53), but some patients also reported symptoms in the periorbital area (n = 19), conjunctiva (n = 8) and in four patients (all with eyelid eczema) lesions extended to the malar region and cheek. In 16 patients, lesions involved more than one of these areas. One patient, an ophthalmologist, had occupational hand dermatitis after manipulating topical drugs.

Of the 65 patients, 44 (67.7%); with a mean age 63.1 years, gave 102 different positive patch test reactions. To the various haptens tested. Most positive reactions were associated with active ingredients (n = 56), especially aminoglycoside antibiotics (n = 27), followed by excipients (n = 24) such as sodium metabisulphite (n = 7).

Overall, there were 56 reactions to 17 different active ingredients, namely antibiotics (n = 34) and local anaesthetics (n = 9), followed by beta-blockers, iodine povidone, adrenergic and anti-muscarinic agents. Aminoglycosides were, by far, the most common antibiotics (n = 27), particularly neomycin (n = 11), gentamycin (n = 7) and kanamycin (n = 6), followed by polymyxin B (n = 3) and chloramphenicol (n = 2). Local anaesthetics were positive in five patients – tetracaine (n = 3) and benzocaine (n = 2), beta-blockers in five – timolol (n = 4) and betaxolol (n = 1) and iodine povidone in six patients. The five patients who reacted to timolol or betaxolol also reacted to eye-drops containing beta-blockers.

There were also positive reactions to topical products tested ‘as is’ (n = 22 of 44 = 50%), mostly containing beta-blockers, but only 5 (= 22.7%) of these reacted to the active ingredient in the topical product.

The authors stated that their study reinforces previous findings in OftACD, such as the older age of onset, and the importance of antibiotics, which contrast with the progressively lower prevalence of excipients.

This study also helped raising awareness for the sensitisation to beta-blockers, which is probably underestimated.

The authors believe that patch test preparations for the diagnosis of OftACD may require protocol optimisation to improve the diagnostic performance.

Utility of Patch Testing and Lymphocyte Transformation Testing in the Evaluation of Metal Allergy in Patents with Orthopaedic Implants

By Logan J Richards, et al
In CUREUS, Volume 11, Issue 9, September 2019, pp 1-11.
https://doi.org/10.7759/cureus.5761

The purpose of this paper was to review the current literature on the utility of Patch Tests (PT) and lymphocyte transformation testing (LTT) in the evaluation of metal allergy in patients with orthopaedic implants, both pre-implantation and post-implantation. The authors focussed on Total Hip Arthroplasty (THA) and Total Knee Arthroplasty (TKA) surgery as these are two of the most common surgical procedures in the USA and worldwide, with over 1,000,000 of these surgeries performed annually in USA.

Implant failure after these procedures occurs due to a number of causes such as infection or mechanical problems, with metal hypersensitivity being an area of growing interest. The nature and mechanism of a causative relationship between metal hypersensitivity and implant failure have been unclear as it is not known whether implant failure occurs due to a previous metal allergy or metal allergy results from secondary sensitisation via metal exposure in existing failing implants. Overall, there appears to be growing support and evidence for metal-hypersensitive patients having worse outcomes with regard to total hip and knee arthroplasties. However, there are conflicting recommendations for pre-implant testing for metal hypersensitivity as testing has not consistently been shown to change patient outcomes.

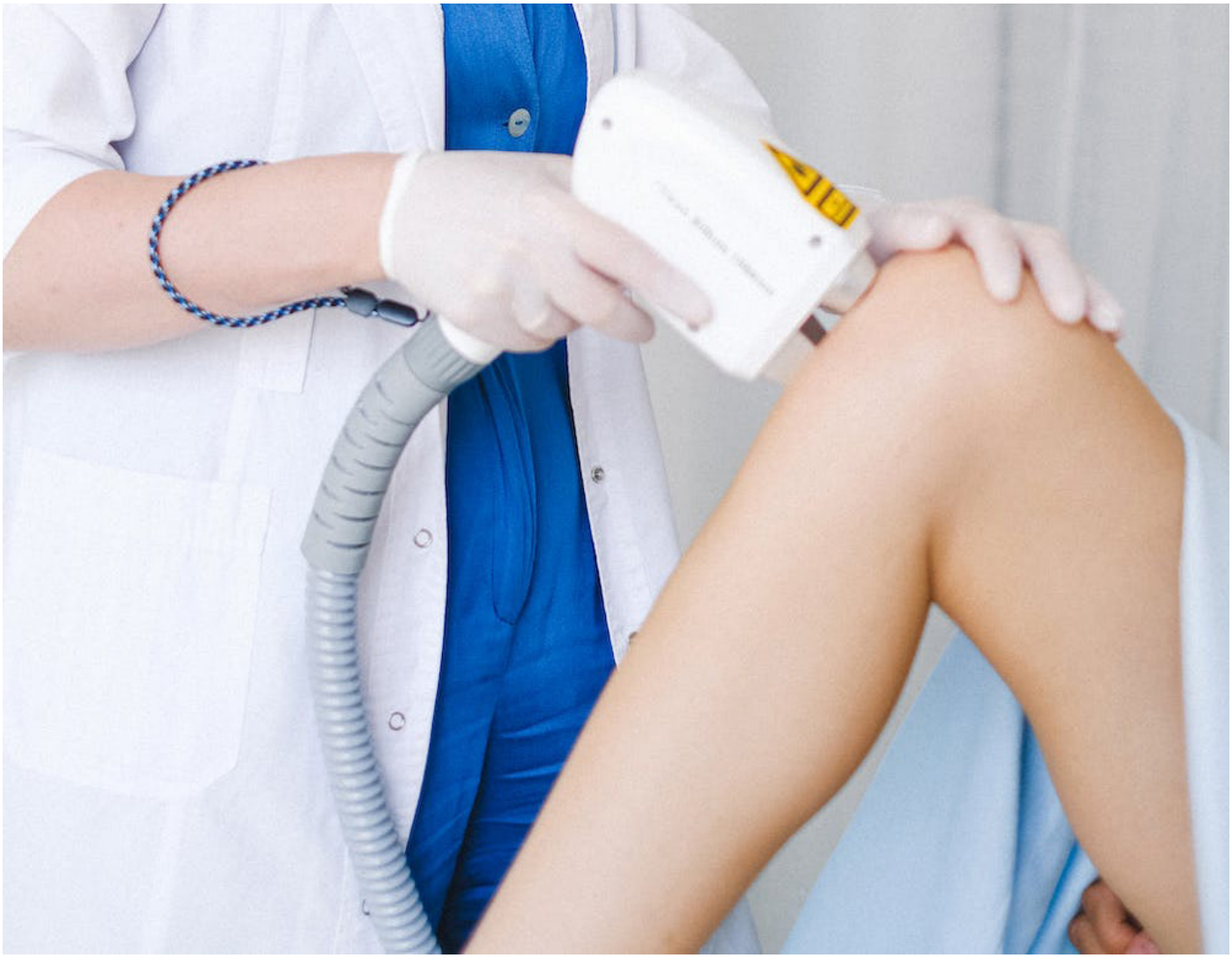
The revision rates for TKAs have remained constant at about 8% to 10%.
Rates of revision surgery for THAs have remained around 20%.

Some of the most frequent causes of orthopaedic implant failure include infection, implant size factors (mechanical issues), and placement issues of the implant. The most common cause of failure, in general, is aseptic loosening, followed by infection as the second most common cause.

Metal hypersensitivity is thought to be a possible cause of implant failure, where the body develops an immune response to the metal in the implant.

Metal hypersensitivity (allergy), as well as the association between hypersensitivity and implant failure, has long been reported, but it is a process that is still poorly understood and managed.

Of note, the prevalence of metal allergy in patients who have undergone THA has been found to be much higher than in the general population; as high as 25% in those with well-functioning implants



and 60% in those with a poorly functioning implant or implant failure.

Metal hypersensitivity in Total Hip Arthroplasty (THA) and Total Knee Arthroplasty (TKA)
It should be noted that metal implant allergy is a diagnosis of exclusion and that, at the single patient level, the presence of metal sensitivity is not necessarily indicative of future implant failure.

Presentation of metal allergy in patients with THA or TKA may vary widely but is usually joint swelling and pain, with overlying dermatitis at the implant site. However, cutaneous reactions are not common in patients who have undergone THA, but any cutaneous hypersensitivity reactions to metal implants are most often eczematous; however, cases of generalised or localised vasculitis and urticaria have also been documented.

It has been found that the average lifespan of a THA was reduced from about 120 months to approx-

imately 78 months in patients with a history of positive metal allergy testing. Furthermore, although complications in metal hypersensitive patients are apparently rare, using implants that contain metals to which a patient is sensitive has been thought to trigger the events that bring about implant failure and thus shorten the lifespan of the prosthesis.

Researchers have previously found that having a sensitivity to one or more metals, in addition to a history of delayed-type hypersensitivity, has an overall negative influence on the outcome of the implant, specifically, THA failure occurs earlier. Positive PT to the relevant metals resulted in shorter hip implant lifespan. In 2012, the same group summarised that there is a significantly higher prevalence of metal sensitisation in patients with metal-on-metal total joint arthroplasty, and clinical outcomes of patients undergoing the surgery may be influenced by their hypersensitivity to the components. However, not all current literature agrees with the premise that metal-hypersensitive patients have worse outcomes, as there are conflicting evidence, data, and conclusions from different studies. Therefore, there is a lack of consensus on the relationship between metal implant failure and metal allergy. However, there appears to be overall growing support and evidence for metal-hypersensitive patients having worse outcomes with regard to THA and TKA, and thus proper management will be the key.

Implant metals

Common metal alloys used in orthopaedic implants are stainless steel (which contains nickel), titanium, and oxidised zirconium.

Stainless steel has been used in surgical practices since the early 20th century. Type 316L stainless steel is commonly used and selected for surgical implants. It is a metal alloy with 17% to 19% chromium and 14% nickel, which allows the metal to become corrosion resistant. However, its components may vary from one manufacturer to another. Molybdenum may also be added to form a protective layer against acid exposure.

Titanium is relatively newer in surgical practice, with its most significant advantage being its equal strength to steel while being about 50% lighter. Nitinol, an alloy with 55% nickel and 45% titanium which releases nickel once implanted, is a highly malleable alloy used frequently in endovascular, cardiac and gynaecological implants, but it is not used in orthopaedic implants. Vanadium may be included in stainless steel or titanium alloys and has an allergenic potential.

Metal hypersensitivity in the Nuss Procedure

An interesting contrast to total joint arthroplasty is the use of Nuss bar implants made of metal which are used to play a purely mechanical/corrective action to treat Pectus excavatum of the rib cage. The Nuss Bar is kept implanted for only 2-3 years. Nuss bars uniquely have allergy testing recommendations based on prior studies. Like other metal implants, metal allergy in Nuss bar patients can present variably, with some of the more common signs being dermatitis and wound infection. Implant failure in Nuss patients is much less likely due to the short amount of time they are left implanted (2-3 years). It has been estimated that metal allergy in Nuss patients may be 2.2% to 6.4%. Due to the morbidity of allergic reactions in patients undergoing Nuss procedure as well as a means of potentially avoiding revision surgery, it has been suggested that PT be used on all patients prior to the Nuss procedure. Moreover, it has also been suggested that if metal allergy testing proves to be positive to metals such as nickel (as is found in steel based Nuss bars), then a titanium Nuss bar should be used instead.

Pathogenesis of metal hypersensitivity and testing modalities
The pathogenesis of metal hypersensitivity reactions is complex and involves predominately Type IV delayed-type hypersensitivity, innate immune responses, cytotoxicity, apoptosis, and local lymphocyte proliferation. In cases of revised TKAs, wherein the cause of implant failure was not infection, misalignment, or malposition, the surrounding tissue was shown to have high levels of T-lymphocytes.

Patch Tests
Patch testing is the most readily available testing modality for metal hypersensitivity and as such is regarded as the gold standard test. It is relatively easy to use and has a low cost, making it the testing modality of choice for contact dermatitis.

LTT
Lymphocyte transformation testing works to detect metal hypersensitivity by the measurement of lymphocytes in peripheral blood that are produced in the span of 7 days following allergen exposure. The ratio of lymphocyte proliferation after allergen challenge to proliferation without allergen is expressed as a stimulation index. Some disadvantages to LTT include high cost, limited availability, the limited number of allergens available for testing, lack of standardisation, inter-laboratory variability, false-negative results in case of processing delay, and difficulty maintaining an appropriate sample for determination of lymphocyte proliferation. It may provide some benefit for indeterminate or negative patch test results in a patient strongly suspected of having metal hypersensitivity.

Evaluation of Metal Hypersensitivity: Pre-implantation
With the exception of the Nuss bar procedure, there are no current recommendations for mandatory pre-implant testing for metal hypersensitivity. This is due to the fact that pre-implant testing has not shown to consistently detect patients that may have a hypersensitivity reaction following joint replacement. However, a significant portion of patients with joint implant failure test positive for metal hypersensitivity on PT or LTT. This finding is complicated by the fact that some patients may develop metal hypersensitivity following placement of an artificial joint, which would not have been detected on pre-implant testing. While utilising titanium or other similar hypoallergenic alloys for arthroplasty is an option advocated by some practice groups, titanium hypersensitivity has been reported post-implantation with symptoms including impaired fracture healing, local eczema, pain, swelling, systemic dermatitis, implant loosening, and failure, all of which have been reported to resolve with implant removal and replacement with a non-titanium implant.

Some experts suggest that broad use of pre-implantation testing based on patient-reported history of metal sensitivity and the use of patch test results to guide preoperative implant selection lacks clinical evidence and may not be feasible from a logistical and cost-efficiency standpoint.

Despite the lack of consensus regarding the utility of pre-implant testing, PT in patients with a demonstrated history of metal hypersensitivity prior to arthroplasty is advocated by some groups.

There is an increased interest among patients and the legal system regarding the possibility of metal hypersensitivity as a cause of joint implant failure, with an increased number of malpractice allegations pertaining to inadequate preoperative allergy assessment and a large number of Google hits for “metal allergy malpractice”.

A very interesting study by Schalock and Thyssen surveyed members of the European Society of Contact Dermatitis (ESCD) and the American Contact Dermatitis Society (ACDS), about their preferences for PT in patients with a history of metal hypersensitivity.

- 54% of responders stated that they would patch test a patient with a history of metal hypersensitivity prior to implant
- 38% would recommend a titanium implant for these patients and would forego testing,
- 8% did not think pre-implant testing was necessary for this patient population.

Their results also demonstrated a difference between European and American members, with ESCD members responding more often (12%) that they would not perform pre-implant PT as compared to ACDS members (4%).

In a survey of ACDS members, 88% reported rarely ever using LTT and 83% favoured PT in the evaluation of patients with metal hypersensitivity reactions.

In one survey of orthopaedic surgeons, only 11% reported routinely screening for metal hypersensitivity, 50% reported rarely referring patients for PT and the remainder stating never considering PT. However, most respondents were likely to choose a different implant in patients who had a positive patch test.

Another study showed consensus among orthopaedic surgeons that PT is not necessary even if metal allergy is suspected, with most proceeding with cobalt-chromium or stainless-steel implants in patients with suspected metal hypersensitivity irrespective of PT results.

Nickel is the most common metal found to be positive on PT in patients with failed implants and in the general patch-tested population. However, it should be noted that, when evaluating a patient with a cutaneous reaction following arthroplasty, hypersensitivity to other materials used in surgery, including bone cement components such as acrylates, benzoyl peroxide, hydroquinone and N,N-dimethyl-p-toluidine; suture materials, implanted and topical antibiotics, should also be investigated and past reactions to these agents should be ascertained prior to surgery.

Evaluation of Metal Hypersensitivity: Post-implantation

There are some defined criteria proposed by an international group of PT physicians for diagnosing metal hypersensitivity reactions post-implantation. Major criteria include cutaneous eruption overlying the metal implant, chronic dermatitis that occurs weeks to months post-implantation, complete recovery after removal of the offending implant and positive patch test results to a metal used in the implant. Minor criteria include treatment-resistant dermatitis, systemic allergic dermatitis reaction, positive LTT to metals, morphology and histology consistent with allergic contact dermatitis, unexplained pain at the implant site and failure of the implant.

There is some debate as to whether patients with long-standing, residual pain following arthroplasty would benefit from post-implant testing. While this pain may be a sign of metal hypersensitivity and indicate a reason for re-operation, there are numerous possible causes besides metal hypersensitivity for pain following arthroplasty. The data on the relation of metal hypersensitivity to post-implant outcome and complications is conflicting. Some studies and case reports have demonstrated that even in patients with patch test verified contact allergy to nickel, the implantation of a nickel-contai-

ning arthroplasty device has caused no significant complications on long-term follow up. Furthermore, it has also been shown that there is no association between pseudo-tumour formation, high serum metal-ion levels and metal hypersensitivity in patients undergoing THA.

However, one case series showed that up to 5% of patients developed metal-related cutaneous complications post-implant, especially in those with chromium sensitivity.

In another small study of 16 patients who required revision surgery due to pain, osteolysis, dislocation and/or loosening, 81% had metal sensitivity as determined by PT or LTT.

A study based on the Danish Knee Arthroplasty Register showed that the prevalence of cobalt and chromium allergy was markedly higher in patients who had 2 or more episodes of revision surgery. As previously mentioned, shorter lifespans of implants were seen in patients with positive patch reactions to metals and a history of metal hypersensitivity, with none of the patients with positive tests for bone cement components having a stable implant at the 10-year endpoint.

Post-implantation testing for metal hypersensitivity is recommended for patients with a history of chronic complications following arthroplasty or signs and symptoms of metal hypersensitivity that persist despite medical therapy.

An important factor to consider during testing post-implant patients is prosthesis-induced sensitisation. It has been recommended that those with cutaneous reactions months following arthroplasty be patch-tested, but that those with functioning prostheses remain in place, regardless of patch test results.

A pragmatic approach may be to use the Schalock and Thyssen criteria to appropriately identify metal hypersensitivity reactions in post-implantation patients, and then combining PT, LTT results and potentially histopathology to identify patients who may benefit from device replacement.

Choosing the right test: PT or LTT?
Given the more widespread availability, the ability to test a variety of potential allergens, and low cost, PT is currently the most widely accepted testing modality for detection of metal hypersensitivity. However, given that PT works by introducing antigens into the dermis to induce a cutaneous reaction, there is some question as to whether PT is an accurate way to mimic the environment of the orthopaedic implant.

In one study, 52 patients with metal hypersensitivity diagnosed by history and patch testing, and 48 patients without metal hypersensitivity, were patch tested with stainless steel and cobalt-chromium-molybdenum antigens. Of the 52 patients with metal hypersensitivity, none reacted to the stainless-steel patch test and 5 reacted to the cobalt-chromium-molybdenum test. Unfortunately, this study did not utilise other forms of testing for metal hypersensitivity to ascertain if modalities besides PT had higher detection rates in this population.

Due to the differences between the cutaneous reactions observed in PT and the peri-implant environment, some have proposed that modalities that detect systemic hypersensitivity, such as LTT, maybe a more accurate way to test for metal hypersensitivity in orthopaedic patients.

A study by Stander et. al. (on page 24 in this issue of The Patch Tester) showed that, while both testing modalities had the same rate of false positives, LTT possibly has a higher sensitivity than PT. While the subjects in this study did not undergo arthroplasty, this study suggests that LTT is possibly a better test to screen cases of metal hypersensitivity. Additionally, since LTT detects metal hypersensitivity based on lymphocyte count in peripheral blood, it is logical that this method of testing may be better suited for hypersensitivity induced by the erosion and breakdown of artificial joints. One could conclude that LTT may be a better option at detecting systemic allergies, while PT may be better at detecting dermal hypersensitivity.

LTT may also be a good option in cases of indeterminate hypersensitivity or in patients with joint failure of an unknown cause since it has higher sensitivity than PT. However, this may be limited by the fact that LTT requires much more time, materials, and expense and is less readily available than patch testing.

While LTT and PT are complementary, they are not equivalent; patients may show metal sensitivity on one testing modality, but not the other.

Summary
In summary, outside of the Nuss bar procedures (with PT being recommended on all patients prior to operating), there are currently no recommendations for mandated pre-implant testing for metal hypersensitivity for procedures including total joint arthroplasties.

Pre-implant testing has not yet been shown to consistently detect patients that may have hypersensitivity to metal following total joint arthroplasty. Moreover, it has not been fully elucidated as to whether an implant failure occurs due to a previous metal allergy or metal allergy results from secondary sensitisation to metal components released in the existing failing implants.

PT is regarded as the gold standard due to its wide availability, although it has been criticised for its inability to mimic the actual environment of the orthopaedic implant. Although LTT has been shown to have a greater sensitivity, limitations with regard to its availability and difficulty in maintaining samples perhaps make this test more useful when PT results are equivocal or contradictory.
Post-implantation testing has been recommended for patients with signs and symptoms of metal hypersensitivity following total joint arthroplasty that persist despite medical therapy, as well as in patients with a history of chronic complications following the procedure.

Editor's Comment: *Although this original article has been especially difficult to review due to the many useful items of information, the Reader is, as always, recommended to read the full original article in* ***Cureus*** *journal.*

Contact Allergy to Cannabis and Related Essential Oils

By Sara Abdel Azim et al
In DERMATITIS, Volume 33, No 6, November-December 2022, pp e69-e70.
See https://doi.org/10.1097/DER.0000000000000869

Allergic Contact Dermatitis to Cannabis is rare, with just one case reported in the literature in the context of plant harvesting. The author of this letter to the editor studied allergens in topical cannabinoid products, finding multiple botanical sensitisers, without considering the allergenicity of cannabis itself.
In this one unique case, terpene analysis was performed to investigate the allergenicity of cannabis, which is of high interest in the current era of legalisation.

Naturally occurring terpene chemicals in cannabis include limonene, linalool, Alpha-pinene, Beta-caryophyllene, and Alpha-humulene. The terpenes found by gas chromatography in this patient's sample of raw cannabis material were as follows, in order of concentration measure in mg/g of the raw cannabis, from 375 mg/g to undetectable.

- Beta-Caryophyllene*
- Eucalyptol*
- Alpha-Bisabolol*
- Alpha-Humulene
- Ocimene
- Myrcene*
- Alpha-Pinene*
- Caryophyllene oxide*
- Limonene*
- Gamma-Terpinene
- Beta-Pinene*
- Linalool*

** Indicates that the compound or its oxidation product(s) are reported to be sensitising.*

The terpenes themselves are relatively non-sensitising until they undergo autoxidation on air exposure to form allergenic compounds. For instance, Beta-caryophyllene, the terpene detected at the highest level in this study, is itself considered non-allergenic; and its major sensitising oxidation product caryophyllene oxide, is considered to be a less potent sensitiser than oxidised limonene and linalool.

As this cannabis product industry expands, more cases of allergic contact dermatitis to cannabis may emerge in relation to recreational, occupational, and potential therapeutic usage. The present case suggests that sensitisation to essential oils may increase risk for cannabis contact allergy.

Further research is needed to elucidate allergens in cannabis, considering the wide variety of strains and topical formulations.

Evaluation of Lymphocyte Transformation Tests as compared with Patch Tests in Nickel Allergy Diagnosis

By Sascha Ständer, et al
In CONTACT DERMATITIS, Volume 76, Issue 4, April 2017, pp 228-234.
See https://doi.org/10.1111/cod.12751

The patch test (PT) is considered to be the gold standard for diagnosing nickel (Ni) allergy. The lymphocyte transformation test (LTT) can also be used to detect Ni sensitisation. However, there is little research and documentation about the correlation of the results obtained by the Patch Test and the Lymphocyte Transformation Test. Therefore, the authors of this article investigated these two test systems in 50 patients with self-reported Nickel sensitisation compared to 50 negative control individuals. The Patch tests were performed with at least a baseline series, whereas the LTT tests were done with different dilutions of nickel sulphate (NiSO4).

- In the patch tests, 2 of 50 controls and 18 of 50 patients with self-reported suspicion of Ni allergy showed positive reactions to Ni.

- In the LTTs at NiSO4 concentration of 2.5 × 10-5 m….
  2 of 50 controls and 26 of 50 patients with self-reported suspicion of Ni allergy showed positive reactions to Ni.

- In the LTTs at NiSO4 concentration of 1 × 10-5 m….
  2 of 50 controls and 17 of 50 patients with self-reported suspicion of Ni allergy showed positive reactions to Ni.

- Sixteen of the 18 history-positive and patch test-positive patients were also LTT-positive; i.e. 88% sensitivity of the LTT.

- Two positive LTT reactors of the 48 PT-negative and history-negative individuals:
  i.e. 96% specificity of the LTT.

In conclusion, the authors stated that performing the LTT with optimised stimulating conditions might be a useful additional tool for the diagnosis of Ni allergy if non-sensitised controls are included.

Editor's Comment: *This study was first published in 2017, so prior to the further development of the LTT into the commercially manufactured MELISA test.*

See the accompanying article "Utility of Patch Testing and Lymphocyte Transformation Testing in the Evaluation of Metal Allergy in Patients with Orthopaedic Implants, by L J Richards et al, in 2019, on page 25 in this 13th issue of The Patch Tester.

Delayed Type Reactions to Perennial Moulds in an Atopic Patient

By Puneet Arora
In DERMATITIS, Volume 33, Atopic Dermatitis Supplement, pp s134 – s136.
See https://doi.org/10.1097/DER.0000000000000855

Delayed-type reactions to aero-allergens have previously been observed, predominantly via the Atopy Patch Test. These reactions have been shown to be true Type IV hypersensitivity reactions with similar immunopathology to those of traditional contact allergens in patients with atopic dermatitis (AD). However, the clinical significance of positive Atopy Patch Test reactions continues to be debated.

The Atopy Patch Test is classically the application of traditionally Type I allergens such as Mites, Moulds, Inhalants and Foods in a classical patch test, with PT chambers and 2-4 days reading times.

The authors of this letter to the Editor report on a patient with rhinoconjunctivitis and perennial allergic asthma, eczematous lesions related to atopy, and specific delayed-type reactions to the perennial mould allergens *Aspergillus fumigatus* and *Penicillium notatum*.

A 32-year-old woman presented to the clinic with 6 months of reoccurring pruritic, erythematous, and itchy rashes on her scalp, bilateral arms, hands, and lower extremities from the midthigh to dorsal feet. Antihistamines and topical steroids did not improve the dermatitis or rhinitis. She reported walking her dogs in wooded areas twice daily, taking Allegra daily for seasonal allergies and used CeraVe products on her hands and forearms.

Skin Prick Tests (SPT) were negative to common allergens, such as dust mites *Dermatophagoides pteronyssinus* and *D. farinae* and moulds Aspergillus fumigatus and Penicillium notatum. Such SPT tests are widely used to identify Type I immediate hypersensitive reactions to such aeroallergens.

Intradermal tests (IDT) revealed an immediate (15 minutes) reaction to *D. pteronyssinus* and *D. farinae* (8-mm papule/erythema) and slightly to the mould Penicillium notatum (8-mm erythema).

Standard series patch testing including 120 common allergens (haptens) were applied to clinically normal and untreated skin on the back of the patient. These patch tests were negative after 2 days and 4 days.

However, at 2 days, there had developed a strongly infiltrated plaque of approximately 6-mm diameter over both IDT test sites for moulds, which persisted on Day 4. There was no such occurrence over the test sites for neither *D. pteronyssinus* nor *D. farinae*, though the latter site showed a borderline positive with approximately 3-mm erythema, with no infiltrate.

A 4-mm punch biopsy was performed on day 4 at the IDT test site of *Penicillium notatum*, which demonstrated T cell–mediated eosinophilic infiltration starting in the dermis (injection site) and extending into the epidermis with initial spongiosis. This is characteristic of a delayed-type hypersensitivity reaction. This drew the conclusion that the patient's sensitivity to moulds was a component of AD, with a clear atopic predisposition.

The patient was initially prescribed topical steroids to manage her atopic symptoms. Four months later, she continued to experience severe symptoms, and dupilumab was considered. Dupilumab is the first biologic medication approved for the treatment of AD. It selectively inhibits interleukins 4 and 13, which are two cytokines that have been linked to the type 2 helper T-cell–mediated immune response in AD.

After 6 months of dupilumab therapy, her itching noticeably reduced, rashes no longer appeared on her lower extremities and hands, and her rhinoconjunctivitis and asthma had resolved.

The effectiveness of dupilumab in this patient clearly showed that she had an extrinsic type of AD with delayed-type hypersensitivity to these mould allergens. The clinical relevance of the mould sensitisation is unclear.

The authors hypothesised that it plays a role as an airborne allergen with aggravation of the dermatitis in air-exposed areas. Moreover, it could impact the respiratory epithelium, causing chronic rhinitis and asthma.

The authors of this letter to the Editor advocated for delayed readings of the Intra-Dermal Test in order to guide treatment in these patients with Atopic Dermatitis.

You are invited to notify us If there is a website you would like to have reviewed in a future issue of The Patch Tester or if there is a society or other website that you would like to have included in these lists.

Dermatology Society Websites

ILDS:	*International League of Dermatology Societies*	www.ilds.org
ICDRG:	*International Contact Dermatitis Research Group*	www.icdrg.org
EADV:	*European Academy of Dermatology & Venerology*	www.eadv.org
ESCD:	*European Society of Contact Dermatitis*	www.escd.org
ACDS:	*American Contact Dermatitis Society*	www.contactderm.org
APEODS:	*Asia-Pacific Envmntl & Occupational Dermatology Society*	www.apeods.org
EAACI SAM:	*European Academy of Allergy & Clinical Immunology*	www.eaaci.org
BAD:	*British Association of Dermatology*	www.badannualmeeting.co.uk
AAD:	*American Academy of Dermatology*	www.aad.org
PDA:	*Pacific Dermatolologic Association*	www.pacificderm.org
APD:	*Association of Dermatology Professors*	www.dermatologyprofessors.org
NDA:	*Nordic Dermatology Association*	www.nordicdermatology.com
GDA:	*German Dermatology Society*	www.derma.de
FSA:	*French Society of Dermatology*	www.sfdermato.org
CDA:	*Caribbean Dermatology Association*	www.caribbeanderm.org
ACD:	*Australian College of Dermatologists*	www.dermcoll.edu.au
NZDS:	*New Zealand Dermatology Society*	www.nzdsi.org
DNA:	*Dermatology Nurses Association*	www.dnanurse.org
DermNET NZ:	*Dermatology Infomation Resource for Patients*	www.dermnetnz.org

Dermatology Meeting Websites

www.eadv.org
www.aad.org
www.dermatologymeeting.com
www.asiaderma.sg
www.dubaiderma.com
www.cairoderma.com

In this thirteenth issue of "The Patch Tester" we are taking a look at the website of the MELISA organisation and their diagnostic test to identify Type IV sensitivity to metals.

MELISA
Diagnostic Test for Metal Sensitivity

www.melisa.org

MELISA (Memory Lymphocyte Immuno-Stimulation Assay) is a blood test that detects Type IV hypersensitivity to metals, chemicals, environmental toxins and moulds.

Prof. Vera Stejskal (1944-2017), Associate Professor of Immunology was the inventor of the MELISA test. She was formerly head of Immuno-toxicology at Astra Pharmaceuticals in Sweden (now known as AstraZeneca), where she played a key role developing Losec, Astra's multi-billion-dollar stomach ulcer drug. She left Astra in 1996 to concentrate full-time on MELISA and became Associate Professor of Immunology at the University of Stockholm. She has written numerous articles on metal allergy and gave frequent lectures. Prof. Stejskal passed away in 2017.

Linda Nelson is the USA-based Managing Director of MELISA since 2005. After witnessing how MELISA testing has helped patients recover from chronic illnesses, she has made it her aim to raise awareness of how metals can induce serious health problems in sensitive individuals. She does this by: encouraging and enabling research, working with licensed MELISA laboratories to develop new applications for testing and by organising international conferences.

This very professionally presented website is a blend of information for medical practitioners and patients/public.

The website is presented in several language version: English, Spanish, Italian, Czech, and Portuguese.

The website offers the subscription to a bi-monthly newsletter.

The website also invites the reader to follow their Facebook page at https://www.facebook.com/melisatesting . This Facebook page is a very professionally presented and frequently updated scrolling story comprising reports on primarily medical publications and case reports from medical professionals and patients.

The website structure is as follows:

Metal Sensitivity

- **FAQ**
- **Metal Exposure**
- **Implant Hypersensitivity**
- **Associated Diseases**
- **FDA Statement and British Society for Ecological Medicine**
- **BSEM Conference Program**

Testing

- **Allergens Tested**
- **Phlebotomy**
- **Sending Blood**
- **Sample Report**
- **MELISA vs LTT**

Patients

- **General Information**
- **Choose Your Location'**
- **US/Canada FAQ**
- **Patient Testimonial**

Research

- **Articles**
- **Case Reports**
- **Research Projects**

About

- **Background**
- **Our Team**
- **Laboratory Licensing**
- **Opportunities**

Contact

- **Head Offices**
- **Clinics Providing Access to MELISA**
- **MELISA Testing**
- **MELISA Laboratories**
- **Contact Form**

Order Test Kit

The MELISA® test (Memory Lymphocyte Immuno Stimulation Assay) measures hypersensitivity to numerous metals, such as mercury, titanium, etc., by placing a series of metals into contact with the white blood cells of the person being tested, and then monitoring the reaction.

MELISA tests the patient's white blood cells against a panel of suspected allergens based on the patient's medical and dental history. The reaction is measured by two separate methods: uptake of radioisotope by dividing lymphocytes and evaluation by microscope. The test report shows the strength of the reaction as a Stimulation Index and lists the most common sources of exposure.

MELISA® is a modified, optimised and clinically validated version of lymphocyte transformation testing (LTT).

The Lymphocyte Transformation Test was originally developed in the 1960s for evaluating histo-compatible class II HLA antigens. The method was then modified for class II antigen typing and also applied extensively to detecting Type IV allergies to drugs, metabolites, infectious organisms and metals. LTT became a common test for detection of allergy to beryllium, nickel, gold, cobalt, chromium and palladium. LTT to beryllium is now accepted as the "gold standard" for diagnosing berylliosis, a lung disease, in USA.

In 1994, Stejskal and colleagues published a modification of the LTT for detecting metal sensitivity – which became the MELISA test. The reason for the development of a modern in vitro testing tool was that Astra, a large *Swedish pharmaceutical company needed a test for the diagnosis of occupational drug allergy for their workers exposed to dust containing beryllium during drug* production.

By optimising of the methodology of LTT, MELISA has improved both the specificity and the sensitivity of the test.

Below are the four major changes that MELISA implements, in contrast with LTT.

- MELISA uses a higher number of lymphocytes per test
- The metal concentrations used have been chosen so that they are non-mitogenic and non-toxic
- The test uses partial depletion of macrophages which restores the lymphocyte-monocyte balance so that it is similar to that in the blood
- In addition to objective determination of lymphocyte proliferation by radio-labelled thymidine, morphological examination gives an additional reading directly on the level of stimulated lymphocytes

The primary clinical application of MELISA is to identify Type IV sensitivity to metals.

MELISA has also been developed to diagnose active infections of Lyme Borreliosis, which appears to be a more accurate test for diagnosing active Lyme disease than standard tests (Western Blot, PCR) particularly in symptomatic patients with serologically ambiguous results.

Whilst MELISA is mainly used to determine metal allergy, the test has also been developed for other substances. Some laboratories routinely test for allergy to gluten, *Candida* and moulds.

There is great interest to develop the test for other substances such as gadolinium, PEEK, pesticides and food allergens.

In its primary clinical application to identify Type IV sensitivity to metals, MELISA can be compared to the role of patch testing to identify sensitivity to metals. Results of studies are varied.

For example, in a 2006 study, 56 symptomatic patients exposed to titanium through dental implants were tested with MELISA. Of the 56 patients tested, 21 (37.5%) were positive to titanium. Conversely all patients were patch test negative to titanium.

Other research studies have also supported the application of MELISA:

Seventy-six percent of chronic fatigue patients in a clinical trial experienced health improvement after removing dental restorations containing allergenic metals, as identified by the MELISA test.

An additional study of patients with autoimmune diseases showed that 71% of those with positive responses in MELISA improved after having their fillings removed.

In a further study, patients with fibromyalgia were tested for allergy to metals with MELISA. By reducing their exposure to metals identified as problematic, significant health benefits were seen. 50% of patients no longer fulfilled the criteria for fibromyalgia diagnosis; the remaining 50% all reported an improvement in their symptoms.

An application form for MELISA Testing is available here.

A sample report is shown here.

There are currently four major limitations to the use of MELISA, irrespective of any questions about its clinical validity:

1. Very few laboratories offer the MELISA test; there are only 4 licensed MELISA laboratories, stated in the www.melisa.org website; in Spain, Israel, Germany and Switzerland. Therefore, patients in North America must have their samples sent to Germany for testing. However it is possible that there may be more though perhaps unlicensed laboratories offering the MELISA test as it is heavily advertised in Spain at least by other laboratories.

2. A relatively large blood sample required, for example 36 ml for testing against 10 metals.

3. The blood sample must be processed and packaged very carefully using special blood collection tubes. The sample must be received by the laboratory offering the MELISA test within ideally 24 and maximum 48 hours of the sampling.

4. The cost of MELISA testing is a major limitation.

Description	**Price ($)**
Kit fee (in USA)	35
1-5 metals	350
6-9 metals	380
10-12 metal	420
13-17 metals	470
18-20 metals	520
>20 metals	+15 each
Transportation fee (FedEx, USA to Germany)	~100

Nevertheless, despite the clinical limitations, the severe practical limitations, the poor local availability, and the adverse cost factor, it does indeed seem that there is a real role to play for the MELISA test, certainly for the identification of Type IV hypersensitivity to metals in orthopaedic and dental implants. As such, the MELISA test can be a useful adjunct to the classical patch test.

Contact Dermatitis / Patch Testing

16th March 2023
34th Annual Meeting ACDS 2023
New Orleans, USA
https://www.contactderm.org/events/acds-annual-meeting

4th – 7th September 2024
16th ESCD
Dresden, Germany
https://escd.org/meetings-courses/

Dermatology - International

1st – 2nd March 2023
7th International Congress on Dermatology
Berlin, Germany
lifescience@Worldcongressforum.com

17th – 21st March 2023
American Academy of Dermatology
New Orleans, LA, USA
https://www.aad.org/member/meetings-education/am23

27th – 29th June 2023
British Association of Dermatologists
ACC, Liverpool, England

27th – 28th July 2023
23rd European Dermatology Congress
Paris, France
eurodermatology@europeanmeets.com

3rd - 8th July 2023
ILDS WCD-2023
World Congress of Dermatology
Singapore
https://www.wcd2023singapore.org/

The webpage at www.waset.org/dermatology-conferences-in-2022 is one potentially very useful source of information of Dermatology congresses in 2023.

WASWT is the World Academy of Science, Engineering and Technology. Their webpage states numerous dermatology-related congresses and conferences for 2023.

A word of warning, as has been stated elsewhere in the dermatology world, we need to be aware of the possibility of wishful thinking, opportunism, obsolescent statements, and even misrepresentations or false advertising for congresses. See https://www.bad.org.uk/events/eventcalendar