

# High frequency of contact allergy to implant and bone cement components, in particular gentamicin, in cemented arthroplasty with complications: usefulness of late patch test reading

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## Summary

**Background.** Arthroplasty patients with complications may be sensitized to implant components.

**Objectives.** To quantify patch test reactions to implant materials in aseptic cemented arthroplasty patients with complications, and to evaluate the benefit of late patch test reading at D6.

**Methods.** Analyses of patch test reactions to baseline series and bone cement components and of the questionnaire-aided histories of 250 consecutive patients with suspected implant allergy were performed. Patch tests were read at D2, D3, and D6.

**Results.** There were 187 positive reactions to the 29 allergens of the baseline series, and 52 to the seven allergens of the bone cement series. Forty-nine of 250 patients reacted to the bone cement series. In contrast to 'early allergens' such as fragrance mix, late reading at D6 increased the number of positive reactions by 11/32 for nickel, 1/5 for cobalt, and 2/4 for chromium. With bone cement components, most reactions were to gentamicin (25 of 250 patients), and 17 of 25 appeared only at D6.

**Conclusion.** Late reading is useful for patch tests with metals and bone cement components. With only D2/D3 readings, 32 reactions to nickel, cobalt, chromium and bone cement components would have been missed. This underlines the utility of late reading in general and in complicated cemented arthroplasty patients, given the unexpectedly high number of gentamicin reactions.

**Key words:** allergy; bone cement; gentamicin; implant; late reaction; metal; nickel; patch test.

Artificial joint replacements are increasingly being performed, and for the large majority of patients this means an improvement in the quality of life. However, with

the increasing use of arthroplasty, a growing number of complications, for example implant failure and subsequent revision surgery, are to be expected. In 2011, the respective numbers of total hip replacements (THRs) and total knee replacements (TKRs) were reported to be 465 034 and 702 415 in the United States, and 232 320 and 168 486 in Germany (1) – approximately 9% of these were complication-related revision operations. Apart from infections and mechanical reasons, adverse reactions to implant components may also account for implant failure (2, 3). Accordingly, allergy to nickel, cobalt and chromium has been found in association with

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implant-related dermatitis, persistent pain and swelling, recurrent effusions, and even aseptic loosening (4, 5). 'CoCrMo' alloy indicates the three major components of the different metals contained in this very frequently used implant alloy: cobalt (~65%), chromium (~28%), and molybdenum (~6%). All of the CoCrMo alloys also contain up to 1% nickel. In addition to alloy metals, bone cement constituents may potentially become relevant allergens (6, 7). Bone cements are typically polymethylmethacrylate (PMMA)-based, and result from mixing a liquid and a powdery component. The liquid contains acrylate monomers [e.g. methylmethacrylate (MMA)], activators (e.g. *N,N*-dimethyl-*p*-toluidine), inhibitors (e.g. hydroquinone), and colorants (e.g. chlorophyll-copper complex). The powder is made of acrylate polymer (e.g. PMMA) and benzoyl peroxide as an initiator (8, 9), so that all acrylate-based bone cements initially contain benzoyl peroxide; antibiotics – commonly gentamicin – are often added to prevent peri-implant infection (10), and radio-contrasting substances (such as zirconium oxide) are added to enhance visibility in radiography. Several of these substances found in bone cement are well-known allergens in other areas of application, for example acrylates in dental medicine (11, 12).

For several years, we have been running an outpatient clinic for suspected metal implant allergy patients. Most of the patients present with otherwise unexplained complicated artificial joint replacement. In the case of cemented arthroplasties, we have regularly included a bone cement test series in our patch test series. In general, two readings of patch test reactions are recommended, for example on D2 and D3 (13). As allergic patch test reactions to certain allergens, for example neomycin, cobalt, and gold salts, are known to potentially appear later (14–16), we decided to perform a third late reading on D6. In this study, we investigated, for the first time, the outcome of an additional late reading and its usefulness in detecting allergic sensitization to implant materials, in a large consecutive series of 250 patients with complications after cemented arthroplasty. On the basis of this study, we report an unexpectedly high number of positive patch test reactions exclusively seen on D6 – in particular to gentamicin, a frequently used bone cement additive.

## Materials and Methods

### Patients

Patch test data from 250 consecutive cemented arthroplasty-bearing patients suspected of having allergic reactions to the implant materials were analysed. The study period was from August 2010 to September 2013.

All 250 patients had a CoCrMo-based arthroplasty (189 TKRs; 61 THRs), 94 without and 30 with known titanium components; in 126, the presence of titanium components was unclear. The mean age was 64.8 years (range, 37–84 years), and 164 (65.6%) patients were female. The majority were patients with a first (primary) arthroplasty – 191 of 250. Fifty-nine patients had already undergone revision of the symptomatic joint, but had (otherwise unexplained) symptoms with the subsequent joint replacement, and were then sent for allergy work-up.

Of the 250 patients, 183 had no other metal implant. Of the 67 patients with other metal implants, 16 had problems with the other implant. Ten symptomatic knee arthroplasty patients had also undergone hip arthroplasty (9 of 10 symptom-free); 18 symptomatic knee arthroplasty patients had also undergone contralateral knee arthroplasty, of whom 8 were also symptomatic. A questionnaire-aided history was taken, and supplemented with information from the surgery protocol and implant passport, if available. Furthermore, a set of standardized questions, that is, the orthopaedic Western Ontario and McMaster Universities Arthritis Index questionnaire, was used to quantify the patient's self-reported view of the artificial joint performance, including items for pain, stiffness, and functional limitation (17). 'Classic' complication elicitors such as infection and mechanical causes had been previously excluded by the referring orthopaedic surgeons.

Our investigation was approved by the local ethics committee.

### Allergens and patch testing

For testing, we used Almirall Hermal patch test preparations and Finn Chambers® on Scanpor® tape (Almirall Hermal, Reinbek, Germany). The substances were applied on the upper back on D0. Testing was started on Tuesdays. In accordance with the German Contact Dermatitis Research Group (DKG) criteria (13), the baseline series with 29 allergens and a routine supplemental series were tested in all patients. The supplemental series also contained neomycin sulfate, among other substances. In addition, a bone cement component series was tested.

*Bone cement component series.* Being available as standardized preparations, the following seven constituents were tested: 2-hydroxyethylmethacrylate 1.0% pet., copper(II) sulfate 1.0% aq., benzoyl peroxide 1.0% pet., gentamicin sulfate 20% pet., hydroquinone 1.0% pet., *N,N*-dimethyl-*p*-toluidine 2.0% pet., and MMA 2.0% pet.

*Patch test reading.* The reading was performed by physicians of the allergy unit, but not by the same physician who

initially saw the patient, in order to exclude an examiner bias. Test reading was performed in accordance with the guidelines of the DKG (13) on D2, D3, and additionally on D6, that is, on Monday of the subsequent week. The reactions reported as positive in this article were reactions classified as +, ++, and +++.

When patients showed a positive reaction to gentamicin sulfate, the records were checked, and – if necessary – the referring orthopaedic surgeon was contacted to ensure that the arthroplasty had been fixed with gentamicin-loaded bone cement.

## Results

### History of contact allergy to metals

Of the 250 patients, 72 had a history of 'problems' (such as pruritus, erythema, and eczema) upon skin contact with metallic articles such as jean buttons, wristwatches, and jewellery. However, only a minority of them had been patch tested in the past. In total, 48 of the 250 patients had been patch tested in the past, for several reasons. Among those 48, 21 had a proven metal allergy: 13 to nickel, 6 to cobalt, 2 to chromium, 1 to copper, 2 to palladium, and 2 to gold (some patients had more than one metal allergy found).

### Patient complaints

The patient arthroplasty-related complaints – sometimes, more than one applied to an individual patient – were pain (90.5%), reduced range of motion (74%), swelling (67.5%), effusions (29%), loosening (16.5%), and arthroplasty-associated eczema (5.5%).

### Patch test reactions

Of the 250 patients, 112 had no patch test reactions. Seventy-three had one reaction, 31 had two reactions, 17 had three reactions, and 17 had four or more reactions (in the last of these, reactions to related allergen preparations, for example related to fragrances, were commonly found).

*Baseline series.* The 250 patients had a total of 187 positive reactions to contact allergens of the baseline series. Among these, 25 appeared beyond D3, and were found only at the D6 reading. The allergens with the most frequently occurring delayed reactions beyond D3 were – apart from a few reactors to formaldehyde and jasmine absolute – potassium dichromate (50%), colophonium and Ylang-Ylang oil (40% each), nickel sulfate (34.4%), and lanolin alcohol (33.3%). With regard to

the three metal implant constituents cobalt, chromium, and nickel, the total numbers of positive reactions were, respectively, 5/250, 4/250, and 32/250. The data are summarized in Table 1.

*Bone cement component series.* A total of 49 of 250 patients reacted to one or more bone cement constituents. Positive reactions were predominantly found for two allergens: gentamicin sulfate (25/250; 10%) and benzoyl peroxide (9%). However, combined reactions to both were found in only 2 patients. Furthermore, only very few patients had positive reactions to other bone cement components. Table 2 gives an overview. In the 25 patients who reacted to gentamicin, it could be confirmed by the implant passport and/or by the referring orthopaedic surgeon that gentamicin-loaded bone cement had been used.

### Increase in the number of positive reactions with an additional D6 reading

Table 3 shows the allergens with newly positive reactions at D6. However, the small sample size may result in an unjustified emphasis on reactions gained at the D6 reading. Thus, we focused only on allergens with positive reactions in at least 4 patients. The greatest number of newly positive reactions to any allergen was observed with gentamicin sulfate, that is, 17 of 25 (68%). The allergen with the second highest number of newly positive reactions was nickel(II) sulfate. Of the 32 positive reactions to this allergen, 11 (34.4%) appeared at D6. For colophonium, newly positive reactions occurred in 4 of 10 patients. Figure 1 shows a representative patient with a newly positive reaction to gentamicin sulfate.

### Analysis of subgroups

We were interested in whether reactivity to neomycin sulfate was paralleled by positive reactions to gentamicin. However, of the 8 patients who reacted to neomycin sulfate, only 2 also reacted to gentamicin. Benzoyl peroxide elicited positive patch test reactions in 23 patients, and gentamicin in 25. In contrast, only 2 patients reacted both to benzoyl peroxide and gentamicin. In addition, global reactivity to bone cement components (49 patients) and implant metals, namely nickel (32 patients), was parallel as only 7 patients reacted to both, implant metals and bone cement components. The overall percentages of patients who were allergic to metals/to any bone cement components were 13.6%/21.5% among the 191 patients with primary arthroplasty, and 20.3%/13.6% among the 59 patients with preceding revision of the symptomatic joint. The overall percentages of patients who reacted to gentamicin and benzoyl peroxide, respectively, were 11%

**Table 1.** Positive reactions to 29 baseline series allergen preparations at D2, D3 and D6 in 250 patients with complicated cemented arthroplasty

| Allergen                                                           | Concentration | Vehicle | D2 | D3 | D6 | Total positive reactions (n) | Positive reactions only at D6 |      |
|--------------------------------------------------------------------|---------------|---------|----|----|----|------------------------------|-------------------------------|------|
|                                                                    |               |         |    |    |    |                              | n                             | %    |
| Potassium dichromate                                               | 0.50%         | pet.    | 0  | 2  | 4  | 4                            | 2                             | 50   |
| Thiuram mix                                                        | 1.0%          | pet.    | 0  | 2  | 1  | 2                            | 0                             | 0    |
| Cobalt(II) chloride.6H <sub>2</sub> O                              | 1.0%          | pet.    | 1  | 4  | 5  | 5                            | 1                             | 20   |
| <i>Myroxylon perei</i>                                             | 25%           | pet.    | 3  | 25 | 9  | 25                           | 0                             | 0    |
| Colophonium                                                        | 20%           | pet.    | 2  | 6  | 10 | 10                           | 4                             | 40   |
| <i>N</i> -isopropyl- <i>N'</i> -phenyl- <i>p</i> -phenylenediamine | 0.10%         | pet.    | 0  | 1  | 1  | 1                            | 0                             | 0    |
| Lanolin alcohol                                                    | 30%           | pet.    | 0  | 2  | 3  | 3                            | 1                             | 33.3 |
| Mercapto mix                                                       | 1.0%          | pet.    | 0  | 4  | 3  | 4                            | 0                             | 0    |
| Epoxy resin                                                        | 1.0%          | pet.    | 3  | 6  | 7  | 7                            | 1                             | 14.3 |
| Nickel(II) sulfate.6H <sub>2</sub> O                               | 5.0%          | pet.    | 5  | 21 | 32 | 32                           | 11                            | 34.4 |
| <i>p</i> -tert-Butylphenol formaldehyde resin                      | 1.0%          | pet.    | 0  | 0  | 0  | 0                            | 0                             | 0    |
| Formaldehyde                                                       | 1.0%          | aq.     | 0  | 0  | 1  | 1                            | 1                             | 100  |
| Fragrance mix I                                                    | 8.0%          | pet.    | 15 | 35 | 27 | 35                           | 0                             | 0    |
| Turpentine                                                         | 10%           | pet.    | 1  | 1  | 1  | 1                            | 0                             | 0    |
| Methylchloroisothiazolinone/methylisothiazolinone                  | 100 ppm       | aq.     | 0  | 7  | 6  | 7                            | 0                             | 0    |
| Paraben mix                                                        | 16%           | pet.    | 1  | 1  | 1  | 1                            | 0                             | 0    |
| Cetearyl alcohol                                                   | 20%           | pet.    | 0  | 0  | 0  | 0                            | 0                             | 0    |
| Zinc diethyldithiocarbamate                                        | 1.0%          | pet.    | 0  | 0  | 0  | 0                            | 0                             | 0    |
| Methyldibromo glutaronitrile                                       | 0.20%         | pet.    | 0  | 5  | 1  | 5                            | 0                             | 0    |
| Propolis                                                           | 10%           | pet.    | 4  | 10 | 6  | 10                           | 0                             | 0    |
| Bufexamac                                                          | 5.0%          | pet.    | 0  | 0  | 0  | 0                            | 0                             | 0    |
| Compositae mix II                                                  | 5.0%          | pet.    | 0  | 1  | 1  | 1                            | 0                             | 0    |
| Mercaptobenzothiazole                                              | 2.0%          | pet.    | 0  | 1  | 1  | 1                            | 0                             | 0    |
| Hydroxyisohexyl 3-cyclohexene carboxaldehyde                       | 5.0%          | pet.    | 0  | 7  | 3  | 7                            | 0                             | 0    |
| 2-Bromo-2-nitropropane-1,3-diol                                    | 0.50%         | pet.    | 0  | 1  | 1  | 1                            | 0                             | 0    |
| Fragrance mix II                                                   | 14%           | pet.    | 1  | 13 | 13 | 13                           | 0                             | 0    |
| Ylang Ylang (I + II) oil                                           | 10%           | pet.    | 0  | 3  | 5  | 5                            | 2                             | 40   |
| Sandalwood oil                                                     | 10%           | pet.    | 1  | 4  | 2  | 4                            | 0                             | 0    |
| Jasmine absolute                                                   | 5.0%          | pet.    | 0  | 0  | 2  | 2                            | 2                             | 100  |

**Table 2.** Positive reactions to seven bone cement components at D2, D3 and D6 in 250 patients with complicated cemented arthroplasty

| Allergen                                  | Concentration (%) | Vehicle | D2 | D3 | D6 | Total positive reactions (n) | Positive reactions only at D6 |    |
|-------------------------------------------|-------------------|---------|----|----|----|------------------------------|-------------------------------|----|
|                                           |                   |         |    |    |    |                              | n                             | %  |
| 2-Hydroxyethylmethacrylate                | 1.0               | pet.    | 0  | 1  | 1  | 1                            | 0                             | 0  |
| Copper(II) sulfate.5H <sub>2</sub> O      | 1.0               | aq.     | 0  | 0  | 0  | 0                            | 0                             | 0  |
| Benzoyl peroxide                          | 1.0               | pet.    | 0  | 23 | 10 | 23                           | 0                             | 0  |
| Gentamicin sulfate                        | 20                | pet.    | 0  | 8  | 25 | 25                           | 17                            | 68 |
| Hydroquinone                              | 1.0               | pet.    | 0  | 1  | 0  | 1                            | 0                             | 0  |
| <i>N,N</i> -Dimethyl- <i>p</i> -toluidine | 2.0               | pet.    | 0  | 0  | 0  | 0                            | 0                             | 0  |
| Methylmethacrylate                        | 2.0               | pet.    | 0  | 1  | 2  | 2                            | 1                             | 50 |

and 10.5% among the patients with primary arthroplasty, and 6.8% and 10.2% among the patients with revised arthroplasty.

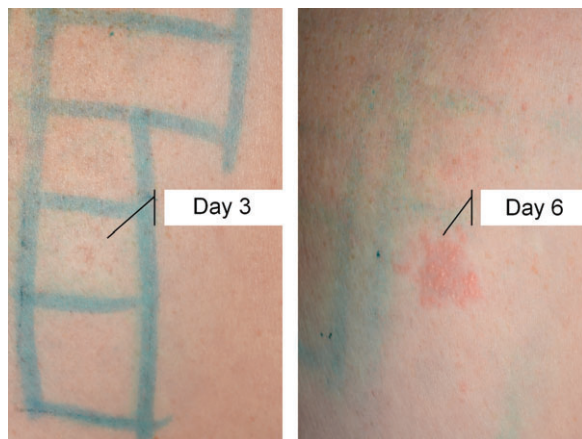
## Discussion

To our knowledge, this is the first investigation assessing the patch test reactions to bone cement components in

complicated cemented arthroplasty in a large patient series. The retrospective analysis showed a high proportion, that is, 49 of 250, of patients with patch test reactions to bone cement components, in particular to gentamicin. Furthermore, the results of this study confirm the high relevance of delayed patch test reading, even though it is more burdensome for older people hindered by arthroplasty complications. With regard to

**Table 3.** Allergens with increases in the number of positive reactions at the late D6 reading, as compared with the D2/D3 reading

| Allergen                              | Concentration (%) | Vehicle | D2/D3 (n) | D6 (n) | Increase (%) |
|---------------------------------------|-------------------|---------|-----------|--------|--------------|
| Potassium dichromate                  | 0.5               | pet.    | 2         | 4      | 50           |
| Cobalt(II) chloride.6H <sub>2</sub> O | 1.0               | pet.    | 4         | 5      | 20           |
| Colophonium                           | 20                | pet.    | 8         | 10     | 20           |
| Epoxy resin                           | 1.0               | pet.    | 6         | 7      | 14.3         |
| Nickel(II) sulfate.6H <sub>2</sub> O  | 5.0               | pet.    | 21        | 32     | 34.4         |
| Ylang Ylang (I + II) oil              | 10                | pet.    | 3         | 5      | 40           |
| Gentamicin sulfate                    | 20                | pet.    | 8         | 25     | 68           |

**Fig. 1.** Positive reactions to gentamicin sulfate (comparison of D3 and D6 readings in the same patient).

gentamicin, more than two-thirds of the allergic patients would not have been identified within the usual testing time span. Further analysis of our data showed that metallic implant constituents, such as chromium, cobalt, and nickel, are also possible 'late allergens'. This is in line with previous reports (14, 15, 18–20). Neomycin sulfate is also well known for its ability to give late patch test reactions (15, 20, 21). However, we observed that reactions to gentamicin sulfate were mostly unrelated to neomycin sulfate sensitization.

In the arthroplasty patients tested here, complications such as pain, recurrent effusions, reduced range of motion, eczema or loosening had not previously been explained by orthopaedic diagnostic work-up. Thus, suspected implant intolerance reactions led to patch testing. However, positive reactions to implant components need to be evaluated for their clinical relevance. First, there should be ongoing exposure to the allergen in question. With regard to chromium, cobalt, and nickel, it is well known that both corrosion and wear particle formation lead to chronic internal exposure (22–24). Bone cement constituents may also be released. Both wear particles – produced by micro-movement of the

implanted device – and leakage of components might account for this. The role of benzoyl peroxide is controversial. Theoretically, it should be consumed by acrylate polymerization, and sensitization should therefore only occur, if at all, upon massive exposure in the course of *in vivo* cementing. Thus, the clinical significance of detected sensitization to benzoyl peroxide needs to be critically questioned. However, the presence of some residual benzoyl peroxide cannot be excluded, as exemplified by analysis of residual constituents such as hydroquinone, MMA and benzoyl peroxide in dental resins/bone cement (25–27). Correspondingly, Bircher et al. described a series of patients with arthroplasty complications, patch test reactions to benzoyl peroxide and symptom relief after bone cement-free arthroplasty replacement (28). However, the high irritative potential of benzoyl peroxide in patch testing has to be considered. On the other hand, as yet unpublished data (summarized in the doctoral thesis of C. Daun) may serve as a comparison: in 112 patients with suspected allergy to dental materials (oral lichen planus, stomatitis, glossodynia, and perioral eczema) tested in our same department in Munich and evaluated by the same staff and in almost the same time period, only two positive reactions to benzoyl peroxide were found. In contrast, gentamicin-loaded bone cement is designed for long-term prevention of periprosthetic infection (29, 30), and gentamicin release is therefore intended. In 1980, Wahlig and Dingeldein reported that, in peri-implant tissue samples, 'high gentamicin concentrations were measurable for a long period of time (up to 5.5 years)' (31). Of course, only a few cases have been reported in which bone cement components such as acrylates, *N,N*-dimethyl-*p*-toluidine, gentamicin or, rarely, benzoyl peroxide were suspected to have provoked arthroplasty complications (6, 7, 32, 33). Second, the clinical relevance of a detected contact allergy should be evaluated. Higher frequencies of cobalt, chromium and nickel allergy have been described in patients with arthroplasty failure than in symptom-free arthroplasty patients (34–36). Some patient series showing symptom relief after revision surgery with alternative/surface-coated implants have

been reported (37–39). By comparing symptom-free and complicated arthroplasty patients with regard to bone cement components, we previously found gentamicin contact allergy to be present only in the latter patient group (36). This observation prompted us to analyse a larger cohort of patients, in whom we extended patch test evaluation to a D6 reading. In the case of detected gentamicin contact allergy, patients were asked whether they recalled having used gentamicin-containing topical medicaments or remember any local ‘problems’ after the use of ‘antibiotic’ eyedrops/ointments etc. (if applied). Finally, in the case of detected gentamicin contact allergy (in 25 patients), we checked the records to ensure that, in those patients, gentamicin-containing bone cement was used. It should be stated that arthroplasty patients – at least in Germany – do not always have an ‘arthroplasty passport’, and are not followed by the same orthopaedic surgeon who initially performed the arthroplasty, so patient records with more detailed information on the materials and type of bone cement used are not always easily available. However, in the case of our patients, information on arthroplasty type and the use of bone cement was compulsory prior to testing. We are well aware that such patients are more time-consuming to follow, and that an additional appointment for a D6 reading is burdensome for them. However, the results presented here emphasize that late reading is important, because many positive reactions – in particular to metals and gentamicin as typical bone cement component – would have been missed completely. This finding may have

important implications, as it supports both a longer period of observation of patch tested patients in general, and considering gentamicin as a potential elicitor of complications in cemented arthroplasty. We would not generally propose changing an arthroplasty on the basis of only a positive patch test reaction. In general, we feel that (i) in patients with symptomatic arthroplasties, ‘common’ aetiologies, such as malpositioning, malalignment, infection, and neurology-related pain should first be excluded by the treating orthopaedic surgeons, and (ii) the severity of symptoms should direct the decision regarding implant exchange. With regard to gentamicin, we can give the patients a medical report indicating that – in the absence of alternative ‘problem elicitors’ – the gentamicin allergy might be a potential elicitor of the patient’s implant complication (under the above-discussed conditions). If the severity of symptoms leads to a decision to perform implant exchange – and this is always to be decided by the treating orthopaedic surgeon – we would recommend the use of bone cement without gentamicin.

Finally, it is encouraging that dermato-allergists can substantially contribute to the interdisciplinary work-up of suspected ‘implant intolerance reactions’.

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