Bone cement associated allergic reaction

A large number of endoprostheses are successfully implanted every year in Germany. More than 230,000 hip endoprostheses and 168,000 knee endoprostheses are implanted, many of which are cemented (1). These surgeries are highly successful and complications are only expected in rare cases. Along with causes such as infections or mechanical problems, symptoms can also be caused by allergies in rare cases. To what extent allergic reactions to ingredients in the bone cement are clinically relevant is currently the subject of scientific studies.

What characteristics indicate allergies to implant materials?

An allergy is defined as an immune reaction by the human body to foreign substances that are actually harmless. However, with an allergic reaction, implants in the human body may cause an inflammatory response with individual variation in the non-specific, peri-implant foreign body reaction. These can lead to osteolysis and/or loosening of implants (3–5).

The triggers for an allergy to implant components are usually the metal alloys used in the implants. Reactions to ingredients in bone cements have only rarely been reported (40). If there is specific sensitisation of the immune system, the presence of potential contact allergens can induce hypersensitivity reactions to implant materials. Typical clinical signs include skin reactions, swelling, pseudolymphoma, wound healing disorders, sterile osteomyelitis or aseptic implant loosening (4, 6–9). Such hypersensitivity reactions are usually T-cell mediated delayed reactions of the immune system (type IV allergy) in which a reaction only starts after hours or days and which are characterised by inflammation at the site of the allergen. (2, 4, 8).

What is the clinical importance of implant-associated allergies?

In regards to metal allergies, it is apparent that implant intolerances due to an allergy occur far more rarely than would be expected from the incidence of sensitisation in the overall population (2). Even with a verified cutaneous metal allergy, applicable metal implants are tolerated in some cases with no reaction (6, 15, 40) and the metal tolerance actual improves in some patients (16). Sensitisation to ingredients in the bone cement is only seen in 0.04 % of patients with endoprostheses (see Tab. 1). Reports of the allergenic potential of bone cement ingredients were published as early as the 1970s. Hypersensitivity reactions such as hand eczema have been verified in medical personnel as a result of using products that contain acrylates or other components of bone cements (e.g. BPO, DmpT) (18–21).

The precise clinical importance of contact allergies against implant materials, such as metals or bone cement ingredients, has not been clarified in terms of possible symptoms associated with endoprosthetic implants with their high risk of complications (22). There are indications of an increase in allergic reactions to the ingredients of bone cements (e.g. the antibiotics that may be present) as well as

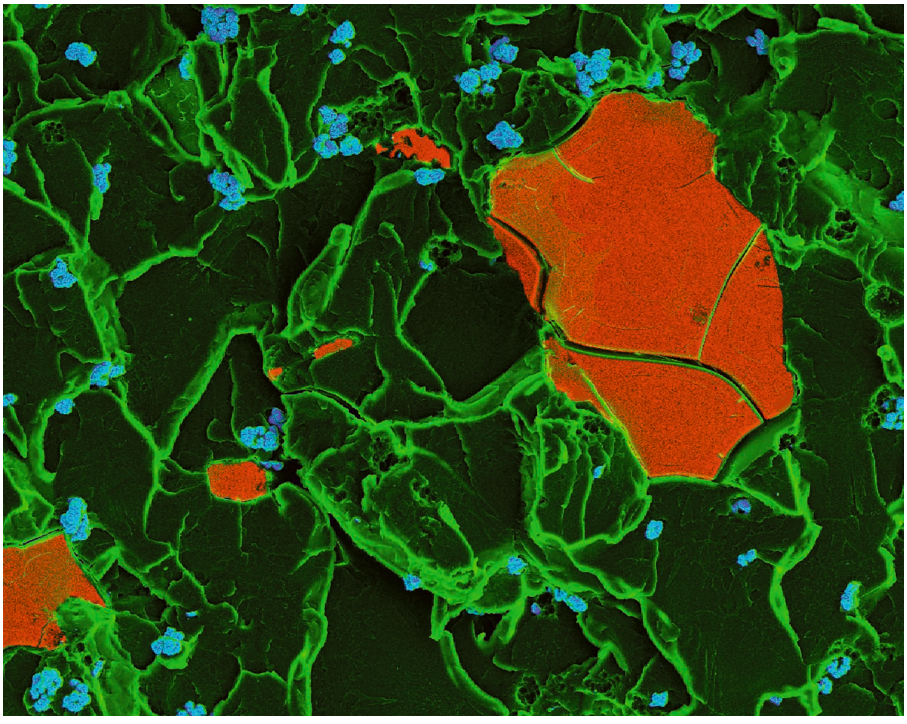

Figure 1. Electron microscope image of PALACOS® R+G (green: bone cement matrix, red: antibiotic, blue: X-ray contrast medium)

descriptions of individual cases (23–26, 41, 43, 44). However, the symptoms only improved and therefore resolved in a very few cases after using a cement-free implant.

What is bone cement made of?

Bone cements based on polymethyl methacrylate (PMMA) are two-component materials made up of a cement powder and a monomer liquid (13) with the composition varying between individual bone cements. The cement powder is made up of polymers, an initiator, an X-ray contrast medium, a colourant and one or more antibiotic(s) where applicable. The monomer liquid is made up of a monomer, an activator, a stabiliser and an optional colourant. Table 2 lists the details of the ingredients for the bone cements produced by Heraeus.

The cement matrix of the set bone cement is can be chemically differentiated from the original bone cement ingredients. During the mixing process, the components react with one another, thus forming the actual bone cement. During the polymerisation process most of the components are either completely converted, consumed or incorporated into the bone cement matrix as a fixed ingredient. (31, 46)

What information is currently available about allergic reactions to the individual ingredients of bone cements?

Benzoyl peroxide (BPO):

There are isolated reports in the literature of allergic reactions to BPO (27, 28).

Sensitivity to	Percentage
Nickel	2.43
Cobalt	0.24
Chrome	0.11
Ingredients in the bone cement	**0.04**

Tab. 1: Frequency of different sensitisations with patients with endoprostheses (40)

Set bone cements from Heraeus Medical have been analysed in accordance with DIN EN ISO 10993-10 (2003 – 02) [Biological evaluation of medical devices; part 10: Tests for irritation and skin sensitisation'] and do not show any sensitising potential.

With a known hypersensitivity to ingredients in bone cements produced by Heraeus, the company recommends avoiding the use of bone cement.

Mass screening revealed a large number of unclear and weakly positive reactions to BPO in epicutaneous tests (29). 9 % of the patients who received an epicutaneous test with BPO 1 % white petroleum jelly showed a weakly positive reaction. However, in most cases this was a false positive result in the form of an irritant reaction (31, 41, 48). This property is used by some acne agents in which BPO is used for external treatment.

In bone cement BPO initiates the polymerisation reaction. It reacts with DmpT and more than 99 % of the substance is bound after the bone cement has set. In the set bone cement, residual quantities can no longer be detected (43, 45). BPO also breaks down to benzoic acid and oxygen on contact with blood or serum (32), meaning that reactions lasting for longer periods can be ruled out (31). BPO is therefore highly unlikely to be a possible cause of allergic reactions to bone cement (31). However, with a known hypersensitivity to BPO that extends beyond mere skin irritation, the use of bone cement should be avoided.

N,N-dimethyl-P-toluidine (DmpT) and hydroquinone:

Neither substance is a potent allergen. During the polymerisation reaction they are quickly consumed. Possible traces of DmpT are neutralised further in the presence of water and oxygen. Hypersensitivity is theoretically possible but actually occurs very rarely and is therefore unlikely in the context of the use of bone cements (31).

Gentamicin, clindamycin and other antibiotics:

The antibiotic that may also be present in the bone cement is released over a longer period. Sensitisation and an allergic reaction are therefore possible in principle (31).

Due to this long-term release, the use of the antibiotic should be avoided with a known hypersensitivity against gentamicin, clindamycin and other antibiotics.

Methyl methacrylate (MMA) and polymethyl methacrylate (PMMA):

Acrylates have allergenic potential. However, the polymer particles are tightly bound in the set bone cement. Any residual monomer is quickly metabolised, cleaved to form carbon dioxide and water and then excreted (45). An allergic reaction is therefore extremely unlikely (41, 43). With a known hypersensitivity to MMA and PMMA, the use of bone cement should be avoided.

Colourant E 141 = chlorophyll-copper complex

As a chlorophyll-copper complex dissolved in vegetable oil, the colourant E 141 has no allergenic potential in principle. The literature describes only very isolated cases of a clinically significant delayed type reaction to copper (33). The E 141 colourant used in the PMMA bone cement is a complex in which the copper ion is tightly bound. Elution of the copper, which would produce a free form that could induce sensitisation, appears unlikely (31). There are no cases reported in the literature of an allergic reaction that could be attributed to traces of peanut oil in the bone cement (34, 42).

Components of the cement powder					
PMMA bone cements	PALACOS® R PALACOS® MV PALACOS® LV	PALACOS® R+G PALACOS® MV+G PALACOS® LV+G PALACOS® fast R+G	COPAL® G+C	COPAL® G+V	COPAL® spacem
Polymer					
PMMA	X	X	X	X	X
Copolymers with MMA	X	X	X	X	X
Initiator					
BPO	X	X	X	X	X
X-ray contrast medium					
Zirconium dioxide	X	X	X	X	
Calcium carbonate					X
Antibiotic					
Gentamicin (gentamicin sulphate)		X	X	X	
Clindamycin (clindamycin hydrochloride)			X		
Vancomycin (vancomycin hydrochloride)				X	
Colourant					
E 141	X	X	X	X	X

Components of the monomer liquid					
PMMA bone cements	PALACOS® R PALACOS® MV PALACOS® LV	PALACOS® R+G PALACOS® MV+G PALACOS® LV+G PALACOS® fast R+G	COPAL® G+C	COPAL® G+V	COPAL® spacem
Monomer					
MMA	X	X	X	X	X
Activator					
DmpT	X	X	X	X	X
Inhibitor/stabiliser					
Hydroquinone	X	X	X	X	X
Colourant					
E 141	X	X	X	X	X

BPO: benzoyl peroxide; DmpT: N,N-dimethyl-p-toluidine; MMA: methyl methacrylate; PMMA: polymethyl methacrylate

Tab. 2: Ingredients of PMMA bone cements from Heraeus (13).

X-ray contrast medium:
Zirconium dioxide, calcium carbonate
The ceramic ingredients of these materials are used as X-ray contrast media. Allergic reactions to these materials are not known (34).

A confirmed allergy to the bone cement used with an endoprosthesis is extremely rare.

- BPO can lead to positive reactions in skin tests although this usually involves irritations. BPO is almost completely consumed during the polymerisation process. The leaching of residual quantities out of the bone cement is extremely unlikely, as has been demonstrated by tests (45, 49).
- Although acrylates do have allergenic potential, reactions are nevertheless rare. Acrylates as triggers of allergies in regards to bone cement are therefore classified as not clinically relevant in the literature (41, 43).
- The other substances present in set bone cement only lead to a positive test reaction in extremely rare cases. An actual allergic reaction is extremely unlikely (41, 43).
- Where applicable, antibiotics can cause allergic reactions in principle. With a known hypersensitivity, a substitute antibiotic or a bone cement without any antibiotics should be used.

Which procedure is recommended with a suspected allergy to ingredients of the bone cement or an implant in general?

Along with precise clarification of any **differential diagnoses** – a periprosthetic delayed infection (low grade or delayed infection) in particular must be ruled out – the initial priority is determining if there is a **history of any allergies**. Previous intolerance reactions to acrylate-based materials such as those present in dental polymers may provide essential information. Other dermatological diseases and even ingredients in disinfectants or skin care products should be considered as competing triggers of an allergy with implant-proximal skin changes. Using specific questionnaires when recording the medical history can be helpful (34).

The **epicutaneous test** is a common routine diagnostic procedure to verify sensitisation to an allergen. However, its use in relation to implant-associated allergies is controversial. The clinical relevance of positive skin reactions with suspected implant intolerances must be critically scrutinised (31). According to a statement by the German Contact Allergy Group (Deutsche Kontaktallergie Gruppe, DKG), if an implant allergy is suspected epicutaneous tests with standard series and expanded implant test series (expanded metal series and bone cement series) are recommended (34). Because of the frequent false positive test reactions, particularly due to BPO, repeat testing and the use of different concentrations and sizes of test chambers are recommended in the literature (41).

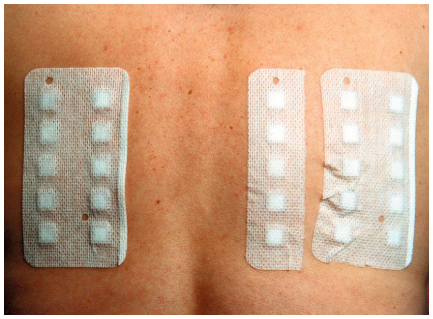

Figure 2: Epicutaneous test on the back

When reading the epicutaneous test, it must be noted that some components (e.g. aminoglycoside antibiotics) only lead to delayed reactions – in some cases up to 7 days later (31, 35, 43, 44). It must also be noted with positive test reactions that contact allergens can also have irritative properties. The result of the later second reading can thus provide important information about whether the issue is really an allergy or actually an irritative reaction of the skin (37).

It is not recommended to carry out preoperative diagnostics using epicutaneous tests because these are not meaningful for predicting a bone cement associated allergic reaction (37, 43, 47).

The **(immuno)histological examination of peri-implant tissue** may provide additional information about the presence of a sensitisation. Formalin-fixed tissue from around the implant enables identification of inflammatory cell infiltrates (particularly with T-cell mediated inflammation), foreign body reactions or infection-related tissue changes. There is no clear definition of a histopathological allergy-induced response pattern (22, 34, 38). However, reference is made to the concurrence of perivascular aggregated lymphocytes and plasma cells, eosinophilic granulocytes, high endothelial venules and fibrin exudate as part of the allergic response pattern (5). In addition, implant-proximal tissue that has been snap frozen or cultured in a special medium can be used to analyse the **cytokine expression profile** of the inflammation, even with a suspected delayed cellular type allergy (22, 34, 38).

The **lymphocyte transformation test** (LTT) may provide additional information about the presence of a type 4 sensitisation. The LTT enables in vitro confirmation of specific, sensitised clones of T lymphocytes after the addition of the antigen to the cell culture. Again, this test only provides supplementary information, even taking the cytokine profile into account, because the relationship between an existing sensitisation and pathological hypersensitivity has not yet been clarified exactly (39). The procedure has also not yet been adequately standardised for widespread use and is not suitable for routine diagnostics.

False positive results in particular should be expected (31).

The diagnosis of an implant-associated allergy should always be based on the assessment of as many diagnostic steps as possible. A thorough medical history, differential diagnosis, clarification of clinical signs, skin tests and the analysis of periprosthetic tissue are required as basics (43).

The diagnosis of 'allergy to bone cement ingredients' or a generalised 'implant allergy' requires a summarising assessment of the findings.

- Clarification of differential diagnoses (differentiation from low-grade infections in particular)
- History of allergies
- Clarification of clinical signs
- Epicutaneous testing (taking particular aspects into account such as frequent false positive results and delayed reactions)
- Peri-implant histopathology

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