

Anaphylaxis to intravenous gentamicin with suspected sensitization through gentamicin-loaded bone cement



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Clinical Implications

- Anaphylaxis to gentamicin is rare. In this case, gentamicin-loaded bone cement is suspected to have caused allergic sensitization to gentamicin and should be considered a new “hidden” allergen.

TO THE EDITOR:

Gentamicin is an aminoglycoside antibiotic used systemically for septicemia and as prophylaxis during surgery. In addition, gentamicin is widely used in bone cement for joint arthroplasty. Delayed type allergy (type IV) to gentamicin has been described¹ and especially delayed type allergy to bone cement is attributed to gentamicin.^{2,3} However, immediate type allergy (type I) to gentamicin is rarely reported, and only 4 cases have been identified in the literature.⁴⁻⁷

We report the fifth case of anaphylaxis to intravenous gentamicin, which to our knowledge is the first case to suggest possible sensitization from previous exposure to gentamicin in bone cement.

A 66-year-old woman was referred to the Danish Anesthesia Allergy Centre (DAAC) for investigation after anaphylaxis with cardiac arrest during elective laparoscopic cholecystectomy. The medical history included asthma, hypertension, and a left knee replacement 4 months previously, but no history of drug allergy.

After anesthetic induction and 5 minutes after intravenous gentamicin, she developed severe hypotension (47/32 mm Hg), bradycardia (45 beats/minute), and desaturation (80%). She was treated with ephedrine, followed by epinephrine and atropine without any effect, and she went into asystole. After 10 minutes of cardiopulmonary resuscitation return of spontaneous circulation was attained. She developed generalized erythema and angioedema and was given antihistamines and steroids on suspicion of anaphylaxis. Surgery was canceled and she was transferred to intensive care where she remained intubated requiring norepinephrine infusion for 2 days. She suffered a cerebral infarction from which she totally recovered. Serum tryptase was markedly elevated at 138 µg/L 3 hours after the reaction.

At allergy workup in DAAC, 2 months later she was tested with all drugs and substances she was exposed to before the reaction including latex, ethylene oxide, chlorhexidine, bupivacaine, dexamethasone, macrogols, remifentanyl, cisatracurium, suxamethonium, propofol, and gentamicin (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Baseline tryptase was 3.6 µg/L. In DAAC, serum tryptase is considered elevated at the time of reaction if the value exceeds $1.2 \times$ baseline value + 2 µg/L.⁸ In our patient, this amounts to 6.32 µg/L, which means tryptase was elevated more than 20 times.

Investigations comprise a combination of skin prick test (SPT), intradermal test (IDT), specific IgE, histamine release test (RefLab, Copenhagen, Denmark), and provocation. Titrated duplicate SPT with gentamicin up to undiluted concentration (40 mg/mL) was positive within 20 minutes showing clear dose response (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Titrated duplicate IDT was clearly positive at a concentration of 0.4 mg/mL. Within minutes, the patient complained of itching on the shoulder and left knee, and wheals were present on the shoulder, and in the scar (Figure 1) from previous left knee replacement 4 months earlier. She developed no other symptoms and the hives resolved completely within 60 minutes with no treatment.

The concentrations used for IDT (max 4 mg/mL) and SPT (max 40 mg/mL) tested negative in 29 exposed controls in our clinic, who all tolerated titrated intravenous provocation with gentamicin up to a maximum dose of 80 mg.

The histamine release test for gentamicin later proved positive and all other substances tested negative in all other tests. Thus, she was diagnosed with immediate type allergy to gentamicin. See Tables E1 and E2 in this article's Online Repository at www.jaci-inpractice.org.

From previous notes we discovered that gentamicin-containing cement (PALACOS R+G cement) was used for her knee prosthesis. She recalled that her left leg had been swollen, red, and itchy postoperatively. Two weeks after surgery, she had been admitted to hospital on suspicion of deep venous thrombosis, which was not found on ultrasound, and infection was also ruled out. Because of unsatisfactory range of movement of the knee, 2 months after surgery, she underwent a manipulation of the joint under general anesthesia.

She reported leaking of clear fluid from the middle of the scar for 3 months after surgery at the same location where the wheal developed during skin testing with gentamicin (Figure 1). Once the wound healed, she had no further problems. Eight months after allergy investigations in DAAC, she had an uneventful right knee replacement without gentamicin in the bone cement and without intravenous exposure.

On detailed questioning, we could not identify other prior exposures to gentamicin or structurally related substances such as neomycin and consider it unlikely, as these drugs are rarely used in Denmark.

We report a rare case of anaphylaxis to gentamicin. Although one earlier case report mentions that the patient had a hip prosthesis,⁵ no cases link previous exposure to bone cement with possible allergic sensitization to gentamicin and anaphylaxis on subsequent exposure.

In our patient, intradermal testing with gentamicin elicited a localized reaction within minutes on the left knee, the site of suspected primary sensitization, separate from skin test sites on the forearm and back, where she also showed strongly positive immediate skin reactions.

Previous exposure to gentamicin-loaded bone cement elicited allergic symptoms possibly due to primary allergic sensitization to gentamicin, as we cannot find evidence of earlier exposure. Alternatively, if she had been sensitized at a prior exposure, it might have been the first manifestation of an immediate type

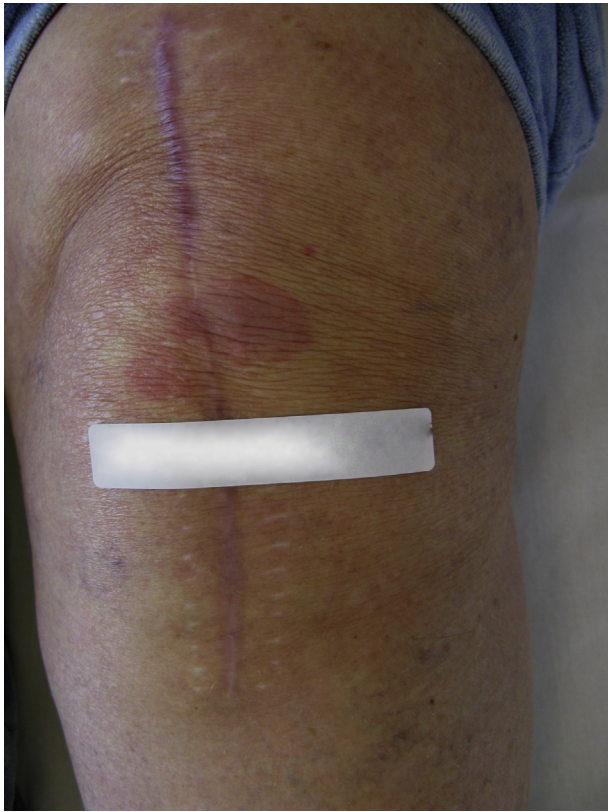


FIGURE 1. Wheal around the scar from knee arthroplasty after skin testing with gentamicin on the forearm and back.

allergy to gentamicin preceding life-threatening anaphylaxis on later exposure, as has been reported in immediate type reactions to chlorhexidine.⁹ If her symptoms after the knee replacement had been recognized as allergic and allergy testing had been performed, she could have been spared a life-threatening reaction. However, the use of gentamicin in bone cement is not well known outside orthopedic surgery and gentamicin might not have been suspected as an allergen on subsequent investigation. This makes it likely that this kind of allergy is underreported.

Combined delayed and immediate type allergy in the same patient has been described for chlorhexidine⁹ and is also described in 2 of the 4 cases of immediate type allergy to gentamicin.^{5,6} In our center, patch tests are never performed if SPT or IDT is positive, and thus we do not know if our patient had a combined immediate type and delayed type allergy. In published cases of delayed allergy to bone cement or gentamicin, most patients were not tested for immediate type allergy.¹⁻³

If the initial symptoms in our patient had been suspected to be delayed type allergy to the prosthesis or bone cement, this might have led to patch testing only and the immediate type allergy might have been missed. Skin prick testing should therefore be

considered in addition to the patch test in patients suspected of any reactions to gentamicin-containing bone cement.

The bactericidal effect of antibiotics in bone cement is known to last days to weeks, but little is known about the long-term allergen exposure. One study found gentamicin in synovial fluid decades after implantation of bone cement when joints were “stressed” with either fractures or prosthesis loosening.¹⁰ The future will show whether situations like these will elicit renewed symptoms in our patient.

Gentamicin has been reported as the antibiotic of choice in bone cement because of the low risk of allergy.¹⁰ A review of the literature suggests that anaphylaxis to gentamicin is indeed rare, but our case illustrates that recognition of early allergy symptoms postoperatively might prevent patients from suffering re-exposure and severe life-threatening reactions.

Allergists investigating perioperative hypersensitivity reactions should always be aware of possible “hidden” allergens, and gentamicin in bone cement has now been added to the list.

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TABLE E1. Test results including maximum concentrations of all drugs in the allergy workup

Test modalities	IgE*	Skin prick test (max conc.)	Intradermal test (max conc.)	Histamine release	Provocation, i.v./s.c. (max dose)
Drug					
Latex	Neg	100 HEP	ND	Neg	ND
Ethylene oxide	Neg	ND	ND	ND	ND
Chlorhexidine	Neg	5 mg/mL	0.002 mg/mL	Neg	ND
Bupivacaine	ND	2.5 mg/mL	0.25 mg/mL	ND	Neg, 5 mg s.c.
Dexamethasone	ND	4 mg/mL	0.4 mg/mL	ND	Neg, 0.8 mg i.v.
Macrogols	ND	Negative	ND	ND	ND
Remifentanyl	ND	0.05 mg/mL	0.005 mg/mL	Neg	Neg, 0.0025 mg i.v.
Cisatracurium	ND	2 mg/mL	0.02 mg/mL	Neg	ND
Suxamethonium	Neg	10 mg/mL	0.1 mg/mL	ND	ND
Propofol	ND	10 mg/mL	1 mg/mL	Neg	Neg, 10 mg i.v.
Gentamicin	ND	40 mg/mL	4 mg/mL	Positive	ND

ND, Not done; Neg, negative; i.v., intravenous; s.c., subcutaneous.

Skin tests are performed in duplicate and titrated in 2 or 3 steps of 10-fold dilution. Thus the lowest concentration is usually 1/100 of the maximum test concentration.

*Values <0.35 kUA/mL are considered negative.

TABLE E2. Skin test concentration for gentamicin and size of skin reactions

Concentration	Skin prick test (wheal, mm)	Intradermal test (reaction, mm)
Negative control (NaCl)	0	8
Positive control (histamine)	8	ND
Gentamicin concentration		
0.4 mg/mL	—	14
4 mg/mL	7	17
40 mg/mL	8	—

ND, Not done.

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