Osteomyelitis treated with gentamicin-PMMA beads

100 patients followed for 1–12 years

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We treated 100 patients having osteomyelitis with debridement and gentamicin-PMMA beads and followed them for 5 (1–12) years. 66 of the infections were chronic, in 18 cases combined with arthritis and in 3 cases with pseudarthrosis. They underwent 117 "treatment periods", consisting of one or more operations (total 152), in most cases with an interval of 2 weeks. No systemic antibiotics were necessary besides the local antibiotic treatment in 52 of the treatment periods. Healing was achieved in 92 patients, in 78 after a single treatment period which included 1–5 operations, in 14 after two or three treatment periods. Healing was more difficult to achieve when the infection was chronic, especially with a duration of more than 6 years or when caused by elective surgery. Local antibiotic treatment with gentamicin PMMA beads has the advantage that the wound can be closed primarily and that a higher local antibiotic concentration in the tissues can be achieved, often making systemic antibiotic treatment unnecessary.

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Since the introduction of gentamicin-loaded polymethylmethacrylate (PMMA) in 1970 (Buchholz and Engelbrecht 1970) and the fabrication of gentamicin-PMMA beads in 1976 (Klemm 1977), antibiotic-loaded bone cement has been increasingly used to prevent and treat orthopedic infections. Beads have proved to be more effective than solid antibiotic-loaded cement plugs in the treatment of osteomyelitis (Vidal and Allieu 1969, Stöhr et al. 1973, Voorhoeve and Stöhr 1973, Jenny et al. 1977, Jenny and Taglang 1979).

We have used gentamicin-PMMA beads since 1982 as the preferential treatment for orthopedic infections. We present the results in patients treated for osteomyelitis with gentamicin beads, who had a minimum follow-up of 1 year after the treatment was completed.

Patients and methods

From April 1982 to April 1996, we treated about 600 patients either closed or operatively for an orthopedic infection. We included in this study the first 100 patients (75 men, aged 47 (13–86) years) with osteomyelitis, who were operated on at least once with use of gentamicin-PMMA beads. They were treated between April 1982 and August 1993. 2 patients had two infections, but only one infected area was included, leaving 100 cases for analysis. In 79 cases the osteomyelitis was isolated, in 18 cases an adjacent joint was involved and in 3 cases pseudarthrosis was present (Table 1). The diagnosis was made by positive bacteriologic cultures or by peroperative findings and

Table 1. Cause and kind of infection, related to recurrences

	O[a]	O+A[a]	O+P[a]	Total	Recurrences	RR
Elective operation	16	6	2	24	8	1
Trauma	45	3	1	49	7	0.4
Hematogenous	15	6	–	21	2	0.2
Decubital	3	3	–	6	0	
Total	79	18	3	100	17	

[a] O osteomyelitis, O+A osteomyelitis and arthritis, O+P osteomyelitis and pseudarthrosis.

Table 2. Duration of infection, related to recurrences

	Total	Recurrences	Interval [a]	RR
Acute infections [b]	34	3	18	1
Chronic cases				
4–11 mo	19	3	28	2.8
1–5 yr	28	5	24	
6–9 yr	3	1	30	5.9
10–19 yr	8	2	33	
20–48 yr	8	3	28	
Total	100	17	26	

[a] Mean symptom free interval in months.
[b] ≤ 3 mo

Table 3. Localization of the infections, related to recurrences

	Total	Recurrences
Femur	16	2
Tibia	29	5
Hip	12	0
Calcaneus	6	2
Ankle joint	7	2
MTP 1	5	0
Other	25	6
Total	100	17

histology. The duration of the disease was 4.5 (0–48) years and 34 infections were acute (duration < 3 months, Table 2). More than half of the infections were posttraumatic (Table 1) and the tibia was the commonest site (Table 3). ß-lactamase-producing *Staph. aureus* was most often found (Table 4), but in 22 cases no causative agent was found (Table 5).

The primary aim of the treatment was to eradicate the infection, and a reconstruction was done secondarily, when necessary. The treatment always consisted of a complete debridement, with sequestrectomy and removal of foreign material, when necessary. Infection after intramedullary nailing was treated with reaming of the medullary canal with 1 mm more than the diameter of the infected nail. As many chains of gentamicin beads as possible were placed in the whole infected area, to achieve maximum gentamicin concentration locally. The chains were made to protrude through the wound, when no further operative treatment was planned, and if not more than 2 short chains were implanted. Chains protruding through the skin were pulled from the wound on the ward: between the 7th and 14th postoperative days about 5 beads a day. When a secondary operation was planned or when more than 2 chains were implanted, the chains were left below the closed fascia and skin. When closure of the skin was not possible, temporary use of artificial skin (Epigard®) was used to prevent leakage of gentamicin. Suction drainage was used for 1 or 2 days but, in case of much bleeding, drains without suction were used. Treatment with systemic antibiotics was also used when the patient was septic or in cases of extensive local soft tissue involvement, and when doubt existed whether the beads covered the whole infected area. If the healing of the infection was unsatisfactory, debridement was repeated every other week, with reimplantation of new beads. Stability was achieved with an external fixator, when necessary. When healing was satisfactory, bony defects were filled with autologous bone grafts at the same time as the beads were removed.

In many cases, one debridement was not enough. Therefore we introduced the concept of "treatment period": one or more operations performed at short intervals, with or without systemic antibiotic treatment at the same time. Such a period could last several months depending on the number of operations. We considered a treatment period of more than 3 months as "prolonged".

Table 4. Causative bacteria

	Number of cultures	
Gram positive bacteria		*63*
Staph. aureus (ß lact+)	34	
Staph. aureus (ß lact–)	6	
Staph. epidermidis	12	
ß-hem. streptococci	5	
Str. faecalis	2	
Streptococci	2	
Staph. saprophyt.	1	
Prop. acnes	1	
Gram negative bacteria		*42*
E.coli	7	
E.cloacae	7	
Klebsiella	6	
Proteus	5	
Pseudomonas	13	
Citrobacter	1	
Salmonella	1	
Flavobacterium	1	
Acinetobacter	1	

Table 5. Causative bacteria related to recurrence and symptom-free interval

	Total	Recurrences	Interval [a]
Negative	22	0	0
Gram positive	48	12	29
Gram negative	17	3	26
Mixed flora	13	2	9
Total	100	17	26

[a] Mean symptom free interval in months.

Table 6. Treatments and operations without (and with) use of systemic antibiotics (AB) related to the recurrence

	Operations		Treatments		Recurrences	
	–AB	+AB	–AB	+AB	–AB	+AB
Large beads	42	56	29	40	7	7
Minibeads	21	17	17	15	2	1
Large + minibeads	5	7	5	7	0	3
Beads + sponges	1	0	1	0	0	0
Sponges	0	3	0	3	0	0
Total	69	83	52	65	9	11
Total ± AB	152		117		20	

The "operations" were interventions during which a (re)debridement was always performed, but sometimes combined with external fixation, bone graft, muscle flap or any other kind of reconstruction. However, operative removal of beads was not registered only as an operation. Healing was defined as absence of clinical signs of infection (sinus, abscess, pain combined with redness and/or fever), normal laboratory findings (ESR, leucocyte counts, CRP) and no recent development of radiographic periosteal elevation or osteolysis. The outcome was considered to be uncertain in patients with periods of intermittent pain, but no other sign of infection.

152 operations were performed in 117 treatment periods. In 149 operations, 10–360 large gentamicin beads and/or minibeads were implanted and, in 4 operations, one or more gentamicin collagen sponges. In 83 operations, systemic antibiotic treatment was also given (Table 6). In 22 operations, artificial skin was used to cover the wound. Another 46 operations were performed just for the removal of beads and were not included in the analysis, In 36, this removal was combined with reconstructive measures.

Data were collected prospectively. The follow-up was performed by regular visits to the out-patient department and by interviewing the patient or his family doctor by telephone. The dates of recurrences were registered and the symptom-free interval was calculated.

Kaplan Meier curves were estimated for the groups defined by diagnosis, duration of infection, cause of infection, localization, causative bacteria, sex, age, and origin of the patient. Groups were compared with the log rank test, Cox regression was used for multivariate analysis.

Results

At follow-up 5 (1–12) years after the completion of the last treatment period, we classified 78 patients as healed after a single treatment period , which included 1 (n 60), 2 (n 15), 3 (n 2) or 5 (n 1) operations. 17 patients had a recurrence. After another 1–2 treatment periods, 14 healed. Thus, 92 cases healed. Healing remained uncertain in 3 patients and 5 did not heal. In 3 of these, a lower leg amputation was performed, but in only 1 patient because of the infection. This patient could not bear the repeated treatments for a pseudomonas infection of the ankle region, and refused further treatment. 1 patient developed a carcinoma cuniculata in a fistula of a calcaneal osteomyelitis, and 1 patient was amputated because of diabetic gangrene.

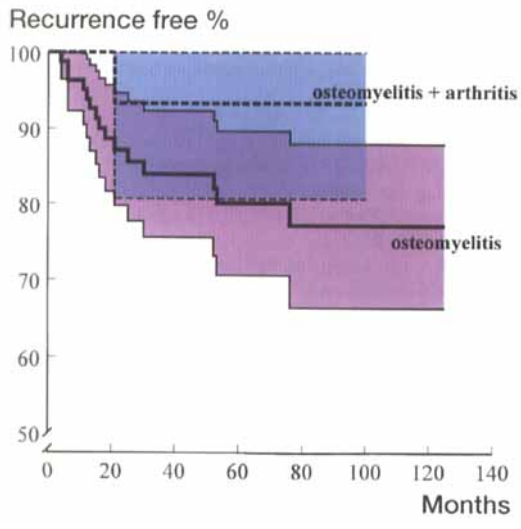
The mean symptom-free interval to recurrence was 26 (4–76) months. Recurrence was commoner in chronic osteomyelitis (14/66) than in acute (3/34). The mean recurrence-free interval was longer in chronic than in acute cases: 28 versus 18 months (Table 2). Cox regression revealed 2 independent factors to be of significance for the symptom-free interval: chronicity and cause of the infection. Concerning the chronicity of the osteomyelitis, the relative risk (RR) of recurrence, after the primary infection had had a duration of 4 months to 6 years, was 3 (95% confidence interval (CI): 0.8–9.9), compared to acute infections. Serious chronicity—i.e., a duration of more than 6 years, had a RR of 6 (95% CI: 1.5–24) compared to acute infections (Table 2).

Concerning the cause of the infection, the relative risk of recurrence due to trauma was 0.4 (95% CI: 0.1–1.0), as compared to infection after elective surgery. Hematogenous or decubital cause of the infection had a RR of 0.2 (95% CI: 0.03–0.7) (Table 1). There was no significant association between the symptom-free interval and sex, age, localization, if systemic antibiotic treatment was used or if the infection was caused by gram-negative bacteria or mixed flora (Table 5).

Because no recurrence occurred in the group of 22 patients with a negative culture, we analyzed their medical records once more. We found that they all had a typical osteomyelitis based on anamnesis, symptoms, peroperative findings and histological examination. In 5 of these patients the negative peroperative cultures could have been caused by antibiotic treatment before the operation.

Discussion

The development of gentamicin-PMMA beads has changed the treatment of orthopedic infections since their introduction in 1976. The local gentamicin release results in a much higher local antibiotic concen-



Fgure 1. Local recurrence after treatment in 100 osteomyelitis cases: in 18 cases combined with septic arthritis of the adjacent joint. Endpoint of all survival curves is 5 cases. Confidence intervals are depicted.

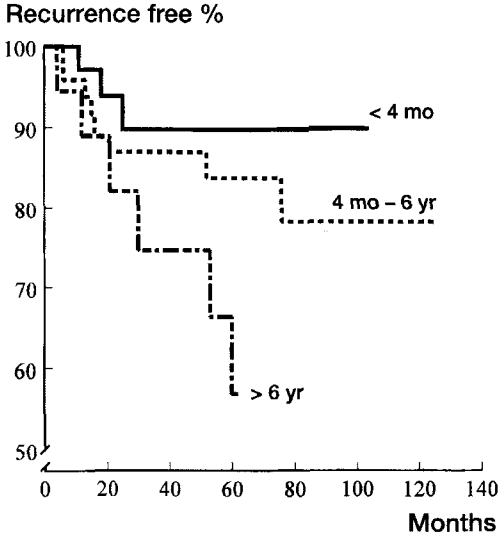


Figure 2. Recurrence-free interval in the 100 cases treated, related to the duration of the infection: 3 months or less, between 4 months and 6 years and more than 6 years.

tration than can be achieved with systemic administration, yet the serum concentration in clinical use remains very low (Hedström et al. 1980, Walenkamp 1983). In animal experiments and in clinical work it has been shown that nephrotoxicity will not be caused by this gentamicin therapy (Giuliano et al. 1986, Walenkamp et al. 1986).

It is difficult to perform a randomized clinical trial of the treatment of osteomyelitis, because the treatment must be individualized. We started such a trial in 1978, randomizing between treatment with gentamicin beads versus suction-irrigation for different kinds of orthopedic infections. After recruitment of 27 patients, the trial was stopped because of more comfort for patients, better wound healing and easier nursing in the group treated with beads, who had similar frequencies of healing (Walenkamp 1983).

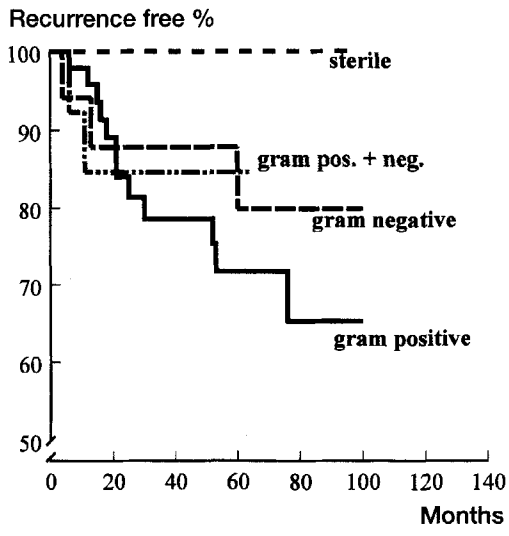


Figure 3. Relation of the causative bacteria and the recurrence-free interval.

In a prospective trial by Hedström et al. (1980) including 48 patients with chronic osteomyelitis or septic arthritis, treated with gentamicin beads or suction drainage, the recurrence rate did not differ, but patients treated with beads were much easier to care for. In another randomized trial with 384 patients, no significant difference in healing percentages could be found between treatment with beads and traditional treatment (Blaha et al. 1993).

A stepwise treatment with repeated debridements at short intervals is valuable, especially in difficult chronic infections. To analyze the results of such a treatment, one must study the results of periods of treatment instead of single operations. With gentamicin-PMMA beads, the wound must be dry at 1 week postoperatively and symptoms of infection markedly improved at 1–2 weeks postoperatively. If this is not the case, further healing cannot be expected by waiting longer, because after 2 weeks the concentration of gentamicin is too low. (Walenkamp et al. 1986, Walenkamp 1989). In that case, another debridement should be performed with implantation of new beads for another 2 weeks. The need for removal of the beads by a second operation is the price for primary closure of the wound. If reconstruction with a bone

graft is needed, the beads will act as a spacer. Beads which protrude through the skin after closure of the wound can be removed gradually on the ward. This, however, is not convenient when several chains are used, when they are 60 beads long or when they are mainly intramedullary.

78 of our 100 patients healed after a single treatment and in 92 after one or more treatment periods. This is in accordance with reports about treatments with gentamicin beads, publishing healing percentages of 90–96% (Vecsei and Barquet 1981, Majid et al. 1985, Cierny 1990, Klemm 1993). Osteomyelitis may, however, recur after many years. The result of the treatment could therefore better be assessed as years until recurrence, i.e., as survival analysis (Figures 1–3). This has not been done before for osteomyelitis. The small number (17) of the observed recurrences caused large confidence intervals, and they are therefore represented in Figure 1 alone. In our analysis. the most difficult cases to treat were the chronic infections. We did not relate the treatment results to the minimal inhibitory concentration (MIC) for gentamicin of the bacteria. Gentamicin resistance in our patients was very rare and did not permit statistical analysis.

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