

## **Infection in massive bone allografts sterilised by radiation**

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**Summary.** *Massive bone allografts sterilised by radiation have been used in our hospital since 1985. The 164 consecutive reconstructions which we carried out before December 1990 were in equal part for tumour resections and revision arthroplasties associated with major bone defects. The allografts were used as intercalary or composite graft-prosthesis reconstructions. Fourteen (8.5%) skin sloughs or infections occurred, all but one after operations for malignant tumours. The grafts never appeared to be responsible. Infection after malignant tumour resection most commonly occurred at the knee when preoperative radiation had been used. Twenty-five reconstructions were performed in the presence of infection, which only recurred in one case. Twelve infections were treated, but 2 other patients died for other reasons within a year. One patient had to have an amputation and one had persistent infection. In the other cases, the infection healed. Only two debridements alone were successful. Removal of the graft and replacement with antibiotic-loaded cement was the most effective treatment.*

**Résumé.** *Les auteurs ont utilisé depuis 1985 des allogreffes massives radio-stérilisées. Des 164 reconstructions successives faites jusqu'à Décembre 1990, la moitié concernait des tumeurs et l'autre des reprises de prothèses avec dégâts osseux majeurs (excluant les petites reconstructions faites avec des têtes fémorales de banque). Il s'agissait de reconstructions intercalaires ou composites (allogreffe-prothèse). Quatorze nécroses cutanées*

*ou infections ont été observées (8,5%). Toutes concernaient des reconstructions pour tumeurs malignes, sauf une, survenue après révision d'une prothèse initialement septique. Les greffes n'ont jamais paru être la cause de l'infection. Le risque septique s'est avéré plus important après résection tumorale et pourtant le rôle de la chimiothérapie n'a pu être prouvé. Des lambeaux de couverture auraient dû éviter les nécroses cutanées qui sont toutes survenues au genou. Vingt-cinq reconstructions ont été faites alors qu'il existait des antécédents d'infection; une seule a récidivé. Douze infections ont été traitées (deux malades étant décédés au cours de la première année d'une cause non infectieuse). Un patient ayant reçu une radiothérapie pré-opératoire a dû être amputé et une infection persiste après un nettoyage simple. Dans les autres cas, l'infection est apparemment guérie, le plus souvent après ablation de la greffe, remplacée temporairement par du ciment imprégné d'antibiotiques, avant reconstruction osseuse secondaire.*

### **Introduction**

From 1955 to 1970, 54 unsterilised frozen allografts were implanted at our hospital, mainly for reconstruction after resection of bone tumours [21, 22, 26]. Infection was the most serious and frequent complication, occurring during the first year in 15 cases, which included 4 with skin sloughing. This led to 4 amputations and the removal of 5 grafts with major shortening of the limb. The use of massive grafts was temporarily abandoned in

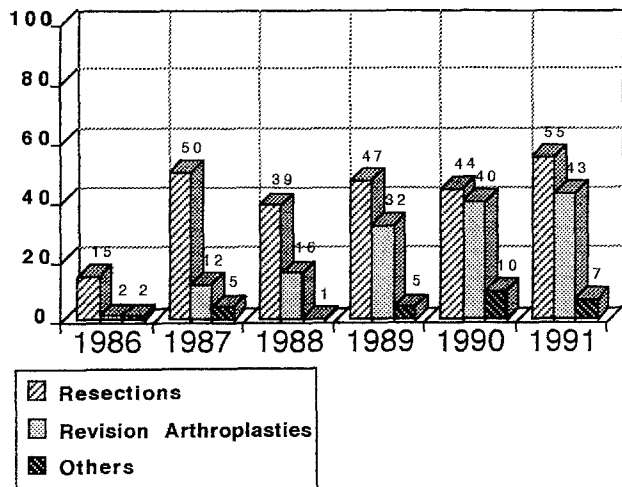


Fig. 1. Radiation sterilized massive allografts: Cochin hospital bone bank activity

Table 1. Total of 164 massive radiation sterilized allografts implanted at Cochin Hospital from 1985 to December 1990

74 revision arthroplasties: (femur or tibia massive reconstructions) (average length of the grafts: 13,5 ± 4 cm)	
69 hips, 5 knees	
55 aseptic revisions, 19 septic revisions	
88 resections: (average length of the grafts: 14 ± 6 cm)	
9 pelvis	
9 humerus	(5 proximal, 3 diaphyses, 1 distal)
24 intercalary lower limb	(7 femurs, 11 tibias, 6 Juvara)
46 composite lower limb	(22 proximal femurs, 5 distal femurs; 19 proximal tibias)
6 benign tumours	
13 revision resections	
69 malignant tumours	(44 with chemotherapy, 25 without)
Osteosarcoma	30
Chondrosarcoma	16
Malignant fibrous histiocytoma	6
Ewing	3
Other bone tumours	9
Metastasis	5
2 others	

1970 because of the high infection rate of almost 30% compared with an overall rate of 2% in the same period.

In 1985, improvement in bone bank procedures [19] and the possibility of sterilising bone [1, 29] led us to use gamma irradiation sterilised bone allografts. From 1985 to the end of 1990, 164 sterilised massive allografts were implanted. These cases have been reviewed retrospectively to determine the incidence and outcome of infection.

## Materials and methods

**Allografts.** These were provided by our hospital bone bank. They were frozen and sterilised by cobalt 60 gamma irradiation at a dose of 25 000 Gy. The bone bank procedure follows the strict guidelines which have already been described [14, 15, 16]. After checking the authorisation for removal, selection of the donor is based on medical history, routine serology including HIV antibodies, antigen and polymerase chain reaction, B and C hepatitis, HTLV, syphilis, cytomegalovirus and a complete autopsy. The graft does not need to be harvested under sterile conditions, but massive contamination is avoided. The grafts are kept frozen before and after irradiation which is carried out at room temperature with precisely controlled dosimetry, avoiding any mechanical damage [14].

Record-keeping is very important in safe bone banking. For each graft information is recorded about the donor's characteristics and serology, conditions of procurement, irradiation dosage and the anatomy of the graft. Details of the recipient, the surgical procedure and the outcome of the graft are always recorded. Computerisation allows stock management, the correct choice of graft for each reconstruction and regular analysis of the efficiency of the procedures.

From 1986 to the end of 1990, 320 massive allografts were distributed by our bone bank to various hospitals, 164 of them being used in the Hôpital Cochin orthopaedic department. The activity diagram (Fig. 1) shows the increased need for revision arthroplasties, whereas the number of tumour resections is now more or less constant.

**Patients** (Table 1). Of the 164 patients having a massive cadaveric bone graft, 110 were female and 54 male with an average age at operation of 48.9 years (range 12 to 88 years).

In 88 patients the allografts were used after resection, mostly for high grade malignant tumours which were receiving adjuvant chemotherapy. The tumours were mostly osteosarcoma, Ewing sarcoma and malignant fibrous histiocytoma. The site of the graft was mainly in the lower limb. In 74 cases, massive cortical allografts were used for revision arthroplasty with major loss of cortical bone. This included 69 total hip replacements with major femoral loss and 5 total knee replacements with femoral or tibial destruction. There were also 2 unclassified cases.

**Surgical technique.** This has already been described [16, 17, 23]. Intercalary reconstruction was usually carried out with intramedullary nails, whereas epiphyseal tumours and revision arthroplasties were dealt with by combining massive allografts with long stemmed endoprostheses. Routine bacteriological specimens were taken in each case from the allograft and the operative wound.

**Antibiotics.** Every patient was given systemic cephamandole and gentamicin during the operation and afterwards for 4 days, followed by oral cephalosporin for 5 days. The endoprostheses were cemented into the allograft and recipient bone with gentamicin-loaded bone cement. Patients with a past history of infection had oral antibiotic treatment for at least 6 months.

**Clinical and radiological examination.** This was carried out at one, 3 and 6 months after operation, and then yearly. Fourteen had a follow up of less than 2 years; 10 had died from complications of the tumour (3 were also infected), another died from unrelated causes and 3 were lost to follow up without known complications. The average follow up was 41 months (range 6 to 79 months).

**Table 2.** Total of 164 massive allografts: 14 infections (8,5%)

74 revis arthroplasties:	1 infection
55 aseptic revisions:	0 infection
19 septic revisions:	1 infection
88 resections:	13 infections
6 benign tumours:	0 infection
13 revision resections:	1 infection
69 malignant tumours:	12 infections
7/44 with chemotherapy (15,9%)	
5/25 without chemotherapy (20%)	

**Table 3.** Risk due to previous infection: only 1/25 recurred

Revision arthroplasties:	
8 infected (1 stage)	1 recurrence
15 previously infected	0 recurrence
Tumors	
1 infected	0 recurrence
1 previously infected	0 recurrence

**Table 4.** Bacteriology (14 infections)

5 staphylococcus epidermidis	3 meti-resistant
5 staphylococcus Aureus	0 meti-resistant
2 streptococcus D	1 multi-resistant
1 corynebacteria	Multi-sensitive
1 multiple organisms	
(Staphylococcus aureus and gram negative)	

## Results

### *Incidence of infection (Table 2)*

There were 14 infections (8.5%). Only one occurred after revision arthroplasty (1.3%), but 13 followed tumour resections (14.7%). These two groups had the same average length of allograft,  $13.5 \pm 4$  cm and  $14 \pm 6$  cm respectively, but the infection rate was significantly different (Fisher exact test  $p = 0.034$ ). No operation for benign tumour became infected, while infection occurred after resection of 12 high grade malignant tumours. Chemotherapy did not have a significant influence; 15.9% of infections occurred in patients with malignant tumours who had pre- and postoperative chemotherapy, and the rate was 20% in those who did not.

Previous infection was responsible for one recurrence (Table 3). Nine patients with previous infection had a single stage reconstruction and 16 had apparently healed infections.

Bacteriological specimens taken from the wound during operation showed a positive growth of staphylococcus epidermis in one case and subsequently an infection developed with the same organism. Specimens from the allografts were all negative.

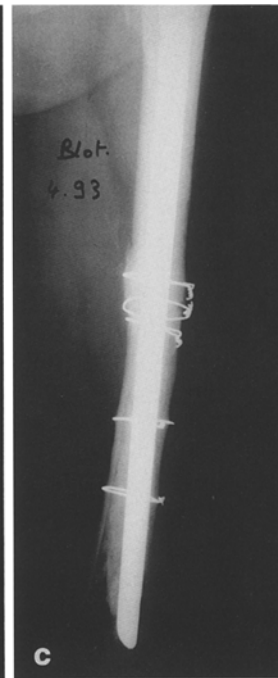
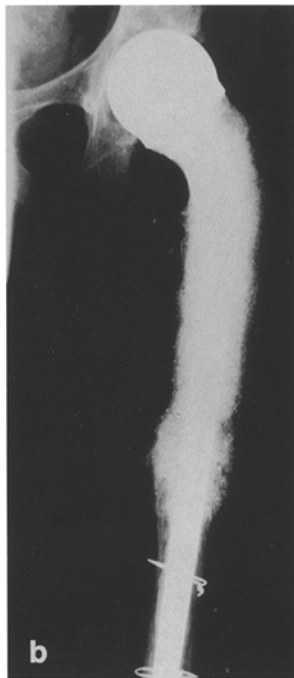
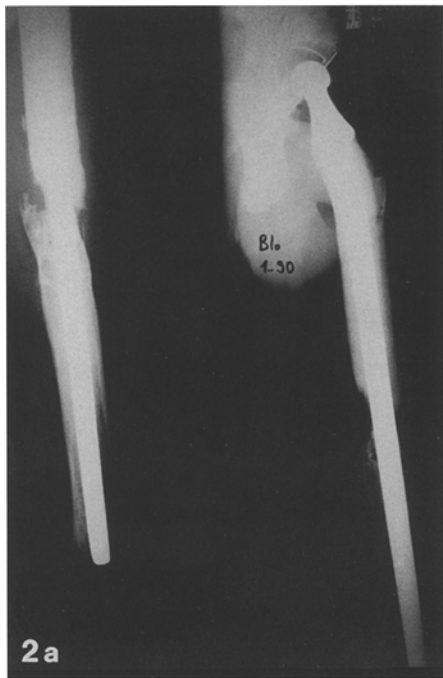
**Table 5.** Nature of the 14 infections

4 post-operative skin sloughs: 4 tibial resections (4/30 = 13%)	
3 upper tibias (3/21 = 20% skin sloughs)	
1 osteosarcoma recurrence after radiotherapy	
1 osteosarcoma + popliteal thrombosis (intra-arterial chemotherapy)	
1 chondrosarcoma	
1 tibial shaft (1/11 = 9% skin sloughs)	
Adamantinoma	
7 early infections (before 6 months):	
1 recurrence after septic THA revision	
6 infections after tumour resection	
1 humerus	osteosarcoma (contaminated operative field)
1 proximal Femur (Composite)	chondrosarcoma (79 years)
1 femoral shaft	osteosarcoma
1 distal Femur (Composite)	massive Prosthesis replacement (infected hematoma)
1 Juvara	osteosarcoma (infected hematoma)
1 Tibial shaft	osteosarcoma
44 chemotherapy:	4 early infections (9%)
25 without:	2 early infections (8%)
3 late infections (after 6 months):	
1 infected trochanteric bursitis	
1 acute infection after minor reoperation	
1 chronic infection (revealed at 3 years)	

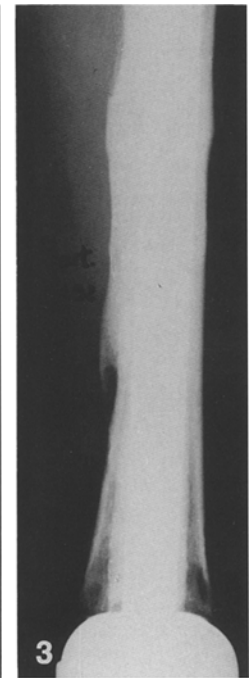
### *Nature of the infection*

All were proved by positive culture (Table 4). A staphylococcus was responsible for most of the infections; four were resistant to many antibiotics, making treatment difficult.

The infection was recognised early, that is before 6 months, in 11 out of 14 cases (Table 5). Postoperative skin sloughing occurred in 4 cases after resection of tumours of the tibia; 3 were composite upper tibial reconstructions and one an intercalary graft. One patient had had radiotherapy (72 Gy) 6 years before, and another had a thrombosis of the popliteal artery after local preoperative chemotherapy. Early infection in 7 cases occurred at various sites including the humerus, the proximal and the distal tibia, and after intercalary grafts in most cases. Two patients had infected haematomas and one had a specimen taken during operation which was positive although the graft specimen was sterile. Four patients had received chemotherapy and two had not, but comparing the 2 groups the early infection rate was the same. In the 44 having chemotherapy there were 4 early infections (9%); in the 25 not having chemotherapy there were 2 early infections (8%). All the early infections in the chemotherapy group occurred during a period of 2 years (1988–1989)



**Fig. 2a–c.** Radiographs of a case of composite reconstruction after resection of a chondrosarcoma. **a** Progressive osteolysis developed and after 3 years there was evidence of frank infection. **b** The graft and endoprosthesis were removed and antibiotic-loaded cement used as a temporary spacer. **c** A new composite reconstruction was carried out after an interval of one year and there were no signs of infection after 2 years



**Fig. 3.** Radiograph of a case of distal femoral composite reconstruction which developed an infected haematoma treated by debridement, irrigation-drainage and long term antibiotics. After 3 years there was no sign of infection. This is an unusually successful outcome of conservative treatment

when a permanent central venous line was used which was subsequently abandoned.

Two late cases presented acutely. One had an amputation at the knee previously and a hip reconstruction for osteosarcoma; he returned to his normal activities, but 2 years later developed an infected trochanteric bursa. The other occurred after a subsequent arthrolysis of the knee.

A chronic infection occurred after a reconstruction of the proximal femur for chondrosarcoma. Radiographs showed progressive osteolysis after one year, and there was obvious sepsis at 3 years (Fig. 2), but no cause was found.

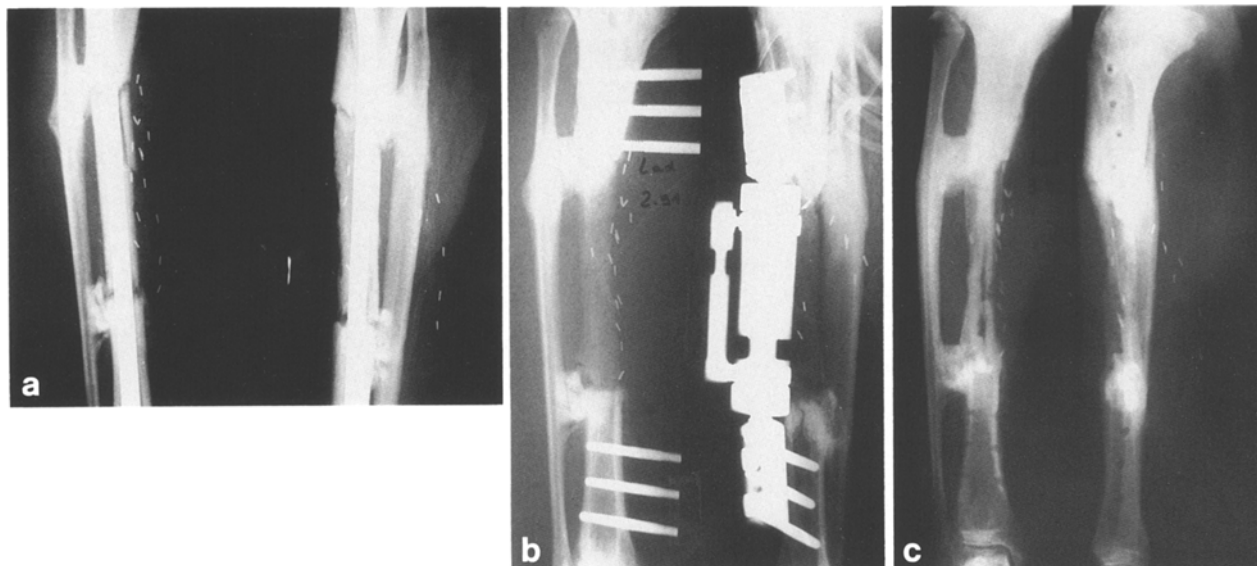
#### *Treatment and outcome*

Two patients with infections died from metastases during the first year. One amputation at the knee had to be carried out in a patient who had received radiotherapy (72 Gy) 6 years previously.

Conservative management was used in 7 early infections and consisted of debridement, irrigation and drainage with local and systemic antibiotics. Infection persisted in 5 patients; 4 had further operations but one, who had metastases, was not

operated on. Only 2 conservative procedures were successful (Fig. 3); in one hip and one knee an early debridement was carried out for acute infection and after 3 years neither have evidence of infection with a good result. In one patient, only the apparently infected part of the allograft was removed and replaced by antibiotic-loaded cement; the infection persisted and a further operation was carried out to remove the graft.

Eight of the infected cases had complete removal of the allograft with maintenance of the length of the limb. In one patient, an autograft and an external fixator were used; 4 further operations had to be carried out with debridement and autografting. Three years later, there is no infection and the tibia is healed, although it is still weak and has a varus deformity. In the other 7 patients, the infected graft was replaced by antibiotic-loaded cement (Table 6). One infected hip was provisionally reconstructed with a long stem endoprosthesis and cement (Fig. 2). One infected composite knee reconstruction was treated in the same way, but 2 others were arthrodesed using a tibio-femoral nail and antibiotic-loaded cement. A nail or external fixator with antibiotic-loaded cement was used in 3



**Fig. 4a–c.** Radiographs of an intercalary tibial reconstruction for an adamantinoma which became infected after sloughing of the skin. **a** The soft tissues were covered by a flap, and a graft between the tibia and fibula was carried out; fusion occurred, but the allograft remained infected. **b** The allograft was removed and replaced with antibiotic-loaded cement and with

stabilisation by an external fixator. A further debridement was carried out a month later and the infection healed. **c** An autograft reconstruction using the opposite tibia was performed one year later. There was no further infection and the radiograph shows that the graft was healed 2 years later

**Table 6.** Fourteen infections: treatment

2 deaths for noninfected reasons, before 1 year
1 amputation: (previous radiotherapy at the knee, 72 Gy in 1979)
7 debridements:
2 success
5 failures: 4 reoperated on
1 chronic infection not reoperated on (metastasis)
1 partial graft resection:
Failure: reoperated on
8 complete graft resections while maintaining the limb length:
1 External fixator followed by autograft (Tibia)
3 Y.: no infection, weak bone reconstruction
7 replacements by antibiotic-loaded cement technique:
4 infected composite reconstructions
– 2 prostheses + antibiotic-loaded cement
– 2 juvara-cement
3 infected intercalary reconstructions:
– 2 nails + antibiotic-loaded cement
– 1 external fixator + antibiotic-loaded cement
Results: infection appeared to heal in all cases
– 3 new allograft reconstructions (after 1 year):
2 apparent success (2 Years)
1 composite proximal femur
1 Juvara
1 infection recurrence (repeated intercalary femoral graft removal)
– 1 autograft reconstruction: apparent success (2 Years)
– 3 still with provisional cement reconstruction
Associated treatments:
Antibiotics systemic treatment at least 6 months
Soft tissue cover repair: 4 flaps

infected intercalary reconstructions (Fig. 4). All patients had appropriate systemic antibiotics for at least 6 months and the infection healed in all the 7 cases. Four new reconstructions were carried out after a year's delay in the absence of evidence of infection, confirmed by aspiration. Three of these procedures, one a composite allograft proximal femoral reconstruction, one Juvara allograft and one tibial autograft, are apparently successful, 2 years after the last operation. In the fourth 2-stage reconstruction, infection recurred at the femoral shaft and the second allograft had to be removed and replaced with antibiotic-loaded cement. The 3 remaining cases, out of the 8 with complete resection of the graft, have no signs of infection, but still have the provisional cement reconstruction.

Muscle flaps were carried out to provide soft tissue cover when necessary.

The results of 12 treated infections are shown in Table 7.

## Discussion

The effectiveness of irradiation depends on the dosage, the nature of the irradiated tissue, the amount of initial contamination and the conditions during irradiation, especially the temperature, since a low temperature stops the sterilising effects of free radicals. Dosage cannot be increased without damaging the strength of the bone [2, 12, 28], and

**Table 7.** 12 treated infections: results

6	healed and reconstructed: 2 after debridement 4 after two-stage reconstruction (antibiotic-loaded cement/graft)
4	healed with provisional antibiotic-loaded cement
1	chronic infection (after debridement)
1	amputation (previous radiotherapy 72 Gy)

a previous study of the preparation procedure in our bone bank showed that there was a 20% decrease in bending strength after 27000 Gy and 35% after 35000 Gy [14]. The bacteriological safety of our procedure has been established [15] using an experimental and statistical method [4]: a  $10^6$  stability assurance level for contamination was achieved after 18500 Gy. The safety of our protocol using gamma irradiation is confirmed in this series and no contamination of the grafts was observed.

We had an infection rate of 8.5%, 6% when skin sloughs are excluded. No infection occurred after aseptic revision arthroplasties or reconstruction after excision of benign tumours, and operations for malignant tumours or the presence of pre-existing sepsis were responsible for all the infections.

Comparison with other reported results must take into account the overall infection rate, the indication for allografting and the follow up. Lord had an infection rate of 11.7% after frozen allograft reconstructions with a follow up of 71 months [13]. Most of his 283 reconstructions were for benign tumours and this infection rate appears high. Tomford's reported incidence was 7% in 190 massive reconstructions, including many revision arthroplasties; the incidence in 96 malignant tumours in his series was 10% [27]. Hernigou had results similar to our own with radiation sterilised allografts [11].

Techniques of tumour reconstruction without using allografts do not appear to have a lower infection rate. Enneking reported 2 infections and 3 skin sloughs (12.5%) after 40 segmental reconstructions with a minimum of 2 year's follow up, but only a few malignant tumours were included [7]. Campanacci had a 19% infection rate in 26 autograft Juvara reconstructions for malignant tumours [3].

Reconstructions using massive endoprostheses were reported to have 15% major infections in 304 operations for bone tumours, including 271 malignant cases [20]. Another similar series had a 7.4% infection rate in bone tumours, 63% of which were of high grade malignancy [25].

The incidence of infection in operations for malignant tumours is obviously high and is generally around 10%. The increased risk has been related to chemotherapy [11, 20]. Our results, and those of others [6, 7, 9, 13, 27], do not confirm this contention.

In tumour resections, the incidence of infection is determined by the wide exposure, soft tissue and vascular injury impairing the host's defences, and systemic antibiotic treatment. The favourable conditions for infection are increased when inert implants, such as endoprostheses [10] or allografts, are used. These circumstances indicate the use of local antibiotics, as was the case with our composite reconstructions. We had an infection rate of 4.3% in composite cases and 12% with uncemented reconstructions, but this was not statistically significant ( $p = 0.39$ ). Precise haemostasis and suction drainage are important to avoid haematomas, which were responsible for 2 early infections in our series.

Skin sloughs all occurred over the tibia and muscle flaps have to be used at this site [11, 12, 20]. Previous radiotherapy is a contraindication to tibial reconstruction.

Reoperations are reported to be a major cause of late infection [13], as was the case in our series. The high risk in these procedures must be recognised when considering the indication, and the need for antibiotic prophylaxis. Prophylactic antibiotic treatment has been suggested for 2 or 3 months until revascularisation of the graft has begun [13], or for 45 days [11], as long as the risk of skin sloughing has been avoided. Nevertheless a shorter period has been shown to be as effective and avoids bacterial resistance [8]. We have found that 10 days' prophylaxis is effective in revision arthroplasties where we had no infections in previously aseptic cases. Previous infection was responsible for only one recurrence of sepsis. Complete surgical debridement was carried out with the use of local antibiotics, and systemic antibiotics for at least 6 months. It is not possible to know whether long term antibiotics would have reduced the infection rate after resections for malignant tumours. The use of antibiotics to which bacteria are sensitive cannot be compared to prophylactic treatment. We believe that treatment for longer than 10 days should only be used when objective risk factors are present.

Amputation was carried out for infection in one case in our series and this was related to damage caused by previous radiotherapy. In 11 cases, the length of the limb was maintained (Table 7); one chronic infection persisted, and 10 appeared to be

healed, 6 of them after having a final bone reconstruction and 4 with a provisional antibiotic-loaded cement spacer.

Conservative treatment, which included debridement, irrigation and suction drainage with antibiotics, or partial removal of the graft, failed except in 2 cases. This type of treatment is only indicated if it is carried out as soon as infection is diagnosed, provided a clean operative field can be obtained and appropriate antibiotics used. In the other cases, complete removal of the graft and temporary reconstruction with antibiotic-loaded cement is a valuable method, together with muscle flaps when there is soft tissue damage. This procedure has been shown to decrease the amputation rate, together with limb shortening. The choice of antibiotics to add to the cement depends of the bacterial sensitivities and often vancomycin has to be added to gentamicin.

Between the 2 stages, we have used antibiotics for at least 6 months after which the second operation is carried out provided that there are no clinical or bacteriological signs of infection. Antibiotic-loaded cement may not be effective after several weeks which is a disadvantage, but there may be benefits from a longer period of curative systemic treatment and an interval with no treatment before the new allograft is carried out. Regimes with 6 weeks between the 2 stages have been reported [13, 24], but the number of cases is too small and follow up too short to come to a final conclusion.

Infection remains the most serious complication after massive bone allograft transplantation and we emphasise the importance of the preventive measures which we have described. Ultraclean air and perioperative antibiotics should be used, with antibiotic-loaded cement in composite reconstructions. Removal of the graft and its temporary replacement with antibiotic-loaded cement is the best method of dealing with deep infection as this makes it possible to preserve of the length of the limb.

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