# Les ciments aux antibiotiques sont-ils utiles en chirurgie prothétique ? NON

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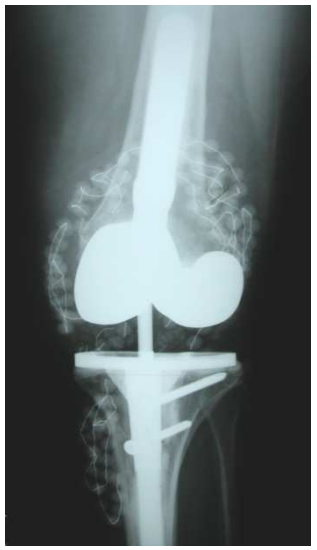
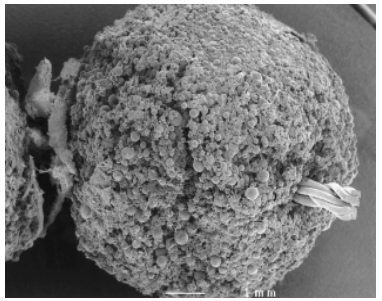
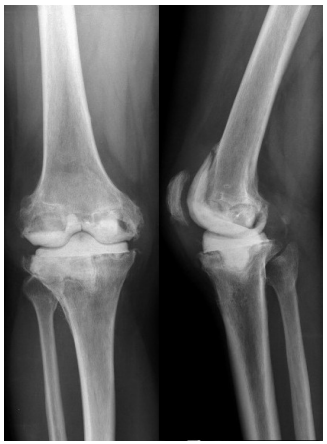






RICAI 2013
33e Réunion interdisciplinaire de chimiothérapie anti-infectieuse

# Ciment aux antibiotiques (AB)

**Polymère: polyméthylmétacrylate (PMMA)**

**Inventé en 1933 (Dr Rohm, Allemagne)**

**Utilisé en orthopédie depuis1958**

***Charnley, JBJS 1960; Buchholz, Chirurg 1970***

**Caractéristiques requises des AB**

- Activité sur germes responsables
- Thermostable
- Soluble dans l'eau
- Peu allergène

***Anagnostakos, Acta Orthop 2006***

***Cui, JBJS 2007***

***RCP IOA sur matériel, SPILF 2009***

**En prophylaxie**

Faible posologie (≤ 1g pour 40g ciment)

***Jiranek, JBJS 2006***

**En curatif**

Forte posologie (> 3.6g pour 40g ciment)

***Anagnostakos, Acta Orthop 2006 ; Cui, JBJS 2007; Hanssen, Clin Orthop Rel Res 2004***

**Indications**

**Changement 2 temps** + spacer AB (genta, vanco +++) = GOLD STANDARD

**Changement en 1 temps** = critère majeur

***Ure, JBJS 1998; Gehrke, Hip Int 2012***

# Ciments AB commercialisés



**Ciment = polymère**

Table 1
Constituents of some commercially available antibiotic-loaded bone cements [26]

| | Antibiotic Simplex[a] Howmedica[b] | CMW 1 Radiopaque G DePuy | CMW 3 G DePuy | Copal Merck | Palacos R-G Schering Plough | Palamed G Merck |
|---|---|---|---|---|---|---|
| *Powder* | | | | | | |
| Poly(methyl methacrylate) | 5.91 | 33.89 | 33.55 | | | |
| Poly(methyl acrylate, methylmethacrylate) | | | | 35.20 | 33.55 | 38.28 |
| Poly(methyl methacrylate, styrene) | 29.51 | | | | | |
| Barium sulphate | 4.00 | 3.60 | 4.00 | | | |
| Zirconium dioxide | | | | 4.72 | 6.13 | 5.28 |
| Benzoyl peroxide | 0.58 | 0.82 | 0.76 | 0.32 | 0.32 | 0.44 |
| Chlorophyllin | | | | | 0.001 | |
| Clindamycin hydrochloride | | | | 1.20 | | |
| Colistin-methane sulfonate-sodium | 0.24 | | | | | |
| Erythromicin-glucoheptonate | 0.73 | | | | | |
| Gentamicin sulphate | | 1.69 | 1.69 | 1.60 | 0.84 | 0.92 |
| Powder total | 40.97 | 40.00 | 40.00 | 42.59 | 40.84 | 44.92 |
| *Liquid* | | | | | | |
| Methyl methacrylate | 18.31 | 18.22 | 17.45 | 18.40 | 18.40 | 18.40 |
| *N,N*-dimethyl-*p*-toluidine | 0.48 | 0.15 | 0.45 | 0.38 | 0.38 | 0.38 |
| Chlorophyllin | | | | 0.0004 | 0.0004 | 0.0004 |
| Hydroquinone | 0.0015 | 0.00046 | 0.00045 | | | |
| Liquid total | 18.79 | 18.37 | 17.90 | 18.78 | 18.78 | 18.78 |

All values are in grams.
[a]This row lists the bone cements.
[b]This row lists the corresponding manufacturers.

**Deux caractéristiques majeurs :**

**STABILITE**

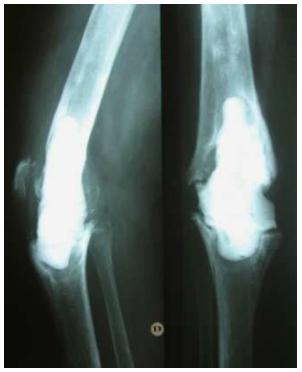
**Pouvoir d'ELUTION des antibiotiques**

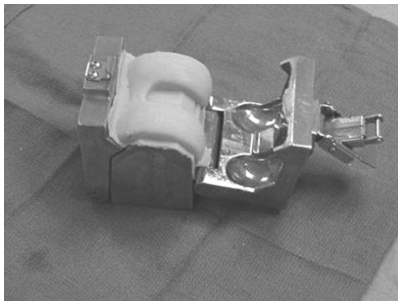
# Propriétés mécaniques du ciment

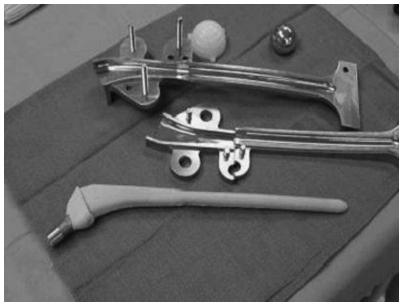
- **Type/forme de spacer AB très variables**
  - Moulage de ciment PMMA (Palacos avec AB, utilisé dans hanche et genou)
  - Tige ou clou formant le squelette entouré de ciment
  - Prothèse enduite de ciment (PROSTALAC)
  - Billes de PMMA

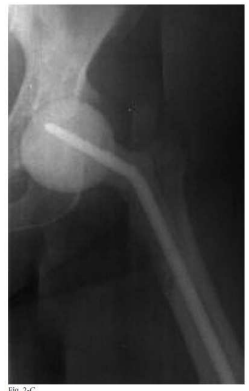
- **Endosquelette métallique pourrait renforcer propriétés mécaniques**
  - Bénéfice clinique insuffisamment étudié
  - Altération de l'élution des AB ?

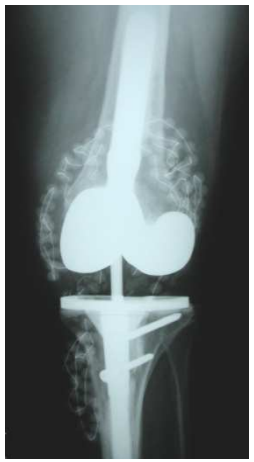
- **Stabilité du ciment et élution de l'AB dépend de nombreux facteurs**

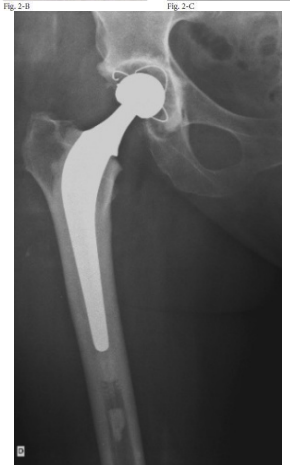












*Hanssen, Clin Orthop Rel Res 2004; Anagnostakos, Acta Orthop 2006; Cui, JBJS 2007*

# Propriétés mécaniques et d'élution des AB du ciment

| | STABILITE CIMENT | ELUTION ANTIBIOTIQUE |
|---|---|---|
| **Type ciment** | + | +++<br>Palacos > CMW, Simplex[1,2]<br>Produit commercialisé > fait « maison » |
| **Conditions de préparation: pression atmosphérique, durée de préparation** | + | +<br>Préparation sous vide avec élution variable selon ciment[3] |
| **Porosité du ciment** | Pores de grande taille, fragilisation | Pores de grande taille : meilleure élution (ex: Palacos) |
| **Surface du spacer** | | ++<br>Grande surface : meilleure élution (billes) |
| **Type, posologie d'antibiotique** | <5% peu d'influence<br>>10% rarement utilisé (diminue stabilité)[4] | ++ |
| **Composition en antibiotiques** | | +++<br>Meilleure élution avec vanco, genta[5,6] |

*1:Buchholz, JBJS 1981; 2:Stevens, J Orthop 2005; 3:Meyer, JBJS 2011; 4:Jiranek JBJS 2006;*

*5: Penner, J Arthoplasty 1996, 6: Masri, J Arthoplasty 1998*

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PROCESSUS COMPLEXES

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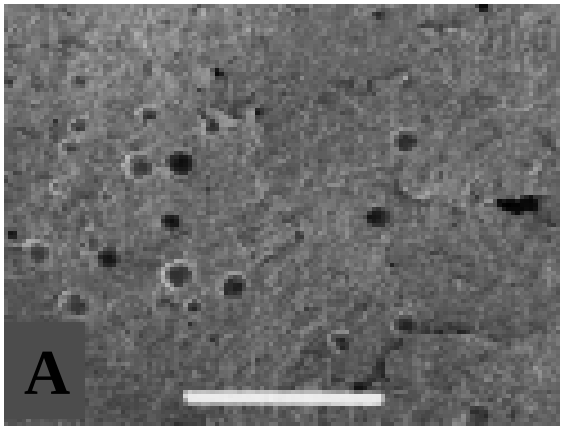
# Porosité du ciment aux AB

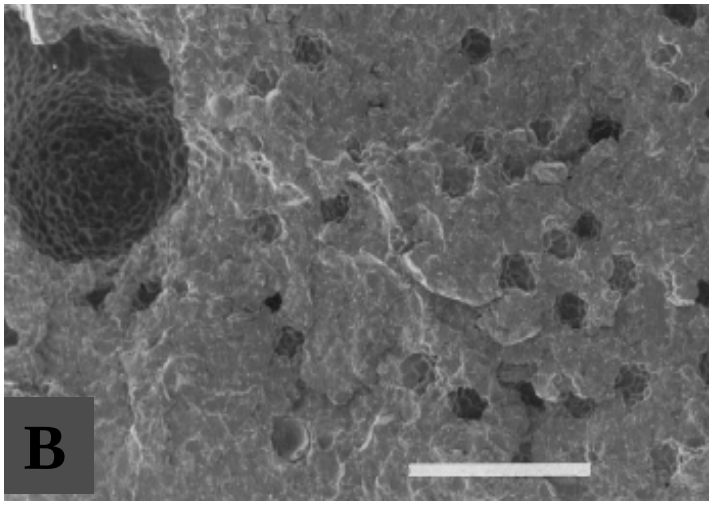


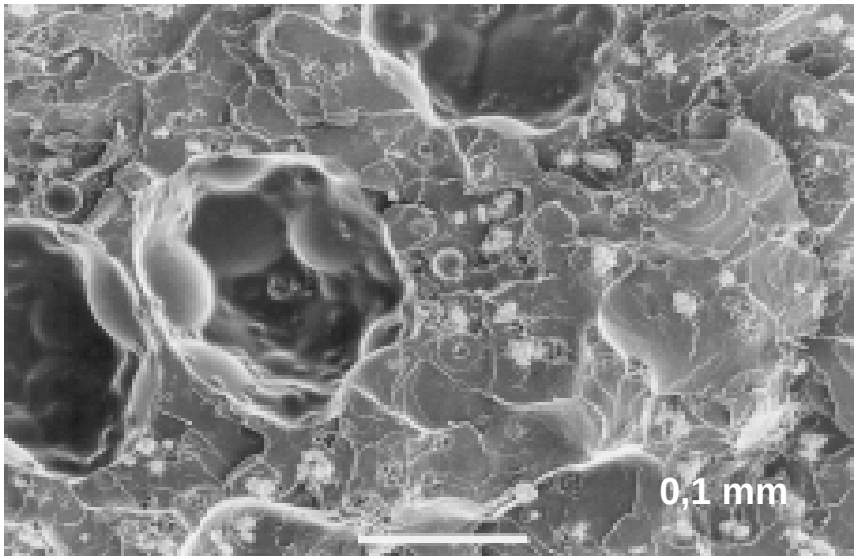

**Microscopie électronique:**

Ciment = polymère

Comparaison de ciment à porosité faible (A) et forte (B)

Présence de pores communicant dans ciment à forte porosité *Neut. Biomaterials 2000*




**Caractéristiques antibiotiques :** thermostable, soluble dans l'eau

# Ciment AB: Elution bimodale

## Etudes *in vitro*

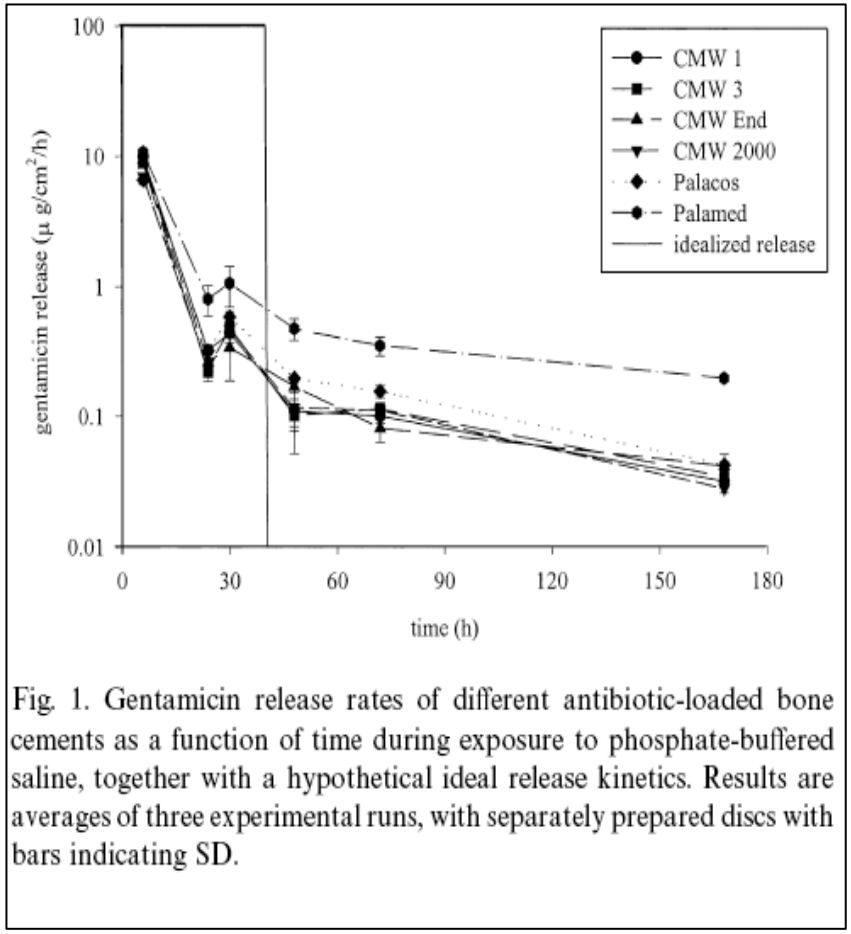
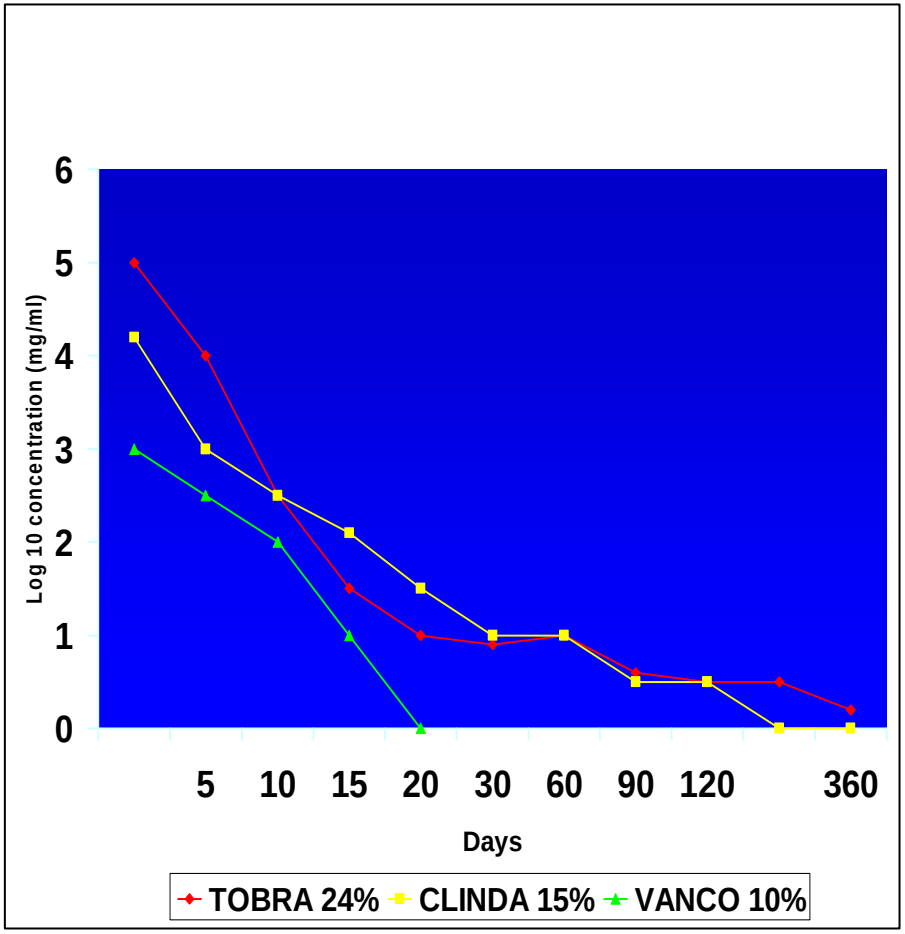



Fig. 1. Gentamicin release rates of different antibiotic-loaded bone cements as a function of time during exposure to phosphate-buffered saline, together with a hypothetical ideal release kinetics. Results are averages of three experimental runs, with separately prepared discs with bars indicating SD.

*Van de Belt, Biomaterials 2000*




*Mader J and al. AAC 1997; 41: 415-418*

**Elution bimodale**

- Deux premières semaines: rapide, puis lente pendant des mois

**10% de quantité d'antibiotique diffusée**

# Ciment AB: Diffusion osseuse faible

Table 2: Gentamicin concentrations in tissues samples (µg/g wet weight) of patients after implantation of Septopal chains (60).

| Patient | Retention time in days | Fibrous tissue | Cancellous bone | Cortical bone |
|---|---|---|---|---|
| P. | 16 | 53.0 | 3.6 | 3.6 |
| H. | 15 | 41.5 | 5.3 | 2.3 |
| H. | 15 | 16.4 | – | 4.5 |
| de V. | 14 | 12.8 | 0.8 | 0 |
| N. | 16 | 18.3 | 1.02 | 0.94 |
| K. | 13 | 48.0 | 2.4 | 0.54 |
| E. | 11 | 10.25 | 0.5 | 1.6 |
| A. | 15 | 25.0 | 16.3 | 2.7 |
| K. | 14 | 115.0 | 36.0 | 3.4 |
| Sch. | 14 | 19.8 | – | – |
| B. | 14 | 39.0 | 3.8 | 2.2 |
| M. | 14 | 16.5 | 5.8 | 1.6 |
| N. | 30 | 33.5 | – | 1.0 |
| C. | 47 | 11.0 | – | 0 |
| N. | 48 | 15.8 | 1.95 | 0.60 |
| H. | 49 | 22.0 | – | – |
| H. | 51 | 16.5 | 1.60 | 0.62 |
| M. | 51 | 9.1 | – | – |
| M. | 53 | 18.7 | – | 0 |
| D. | 63 | 10.0 | 4.3 | 3.0 |
| H. | 70 | 25.0 | 3.3 | – |

*Wahlig 1978*

**21 patients (billes genta)**

CMI gentamicine (µg/ml):

*Staphylococcus* genta S <0,25

*Staphylococcus* genta R 8-64

# Ciment AB: Effet sur formation biofilm

Gentamicin release from PMMA bone cement and *S. aureus* biofilm formation

*Van de Belt, Acta Orthop Scand 2000*

Eude *in vitro*

Incubation de *S. aureus* avec disque de ciment sans et avec gentamicine

Développement du biofilm en présence de gentamicine (en rouge)

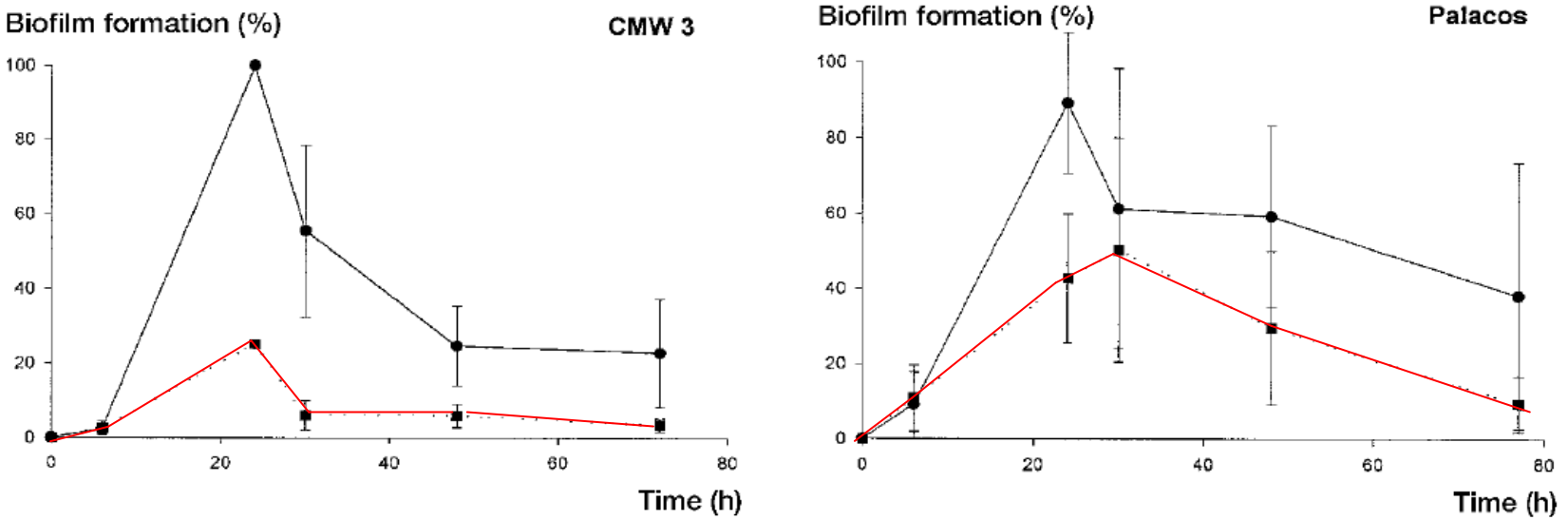



Figure 1. The numbers of infectious *S. aureus* (CFU/cm$^2$) isolated from unloaded (●) and gentamicin-loaded CMW3 (left graph) and Palacos R (right graph) bone cement (■) as a function of time, expressed relative to the maximal number of CFU/cm$^2$ isolated from an unloaded cement disc per run. Results presented are averages of 3 different experimental runs with bars indicating the SD.

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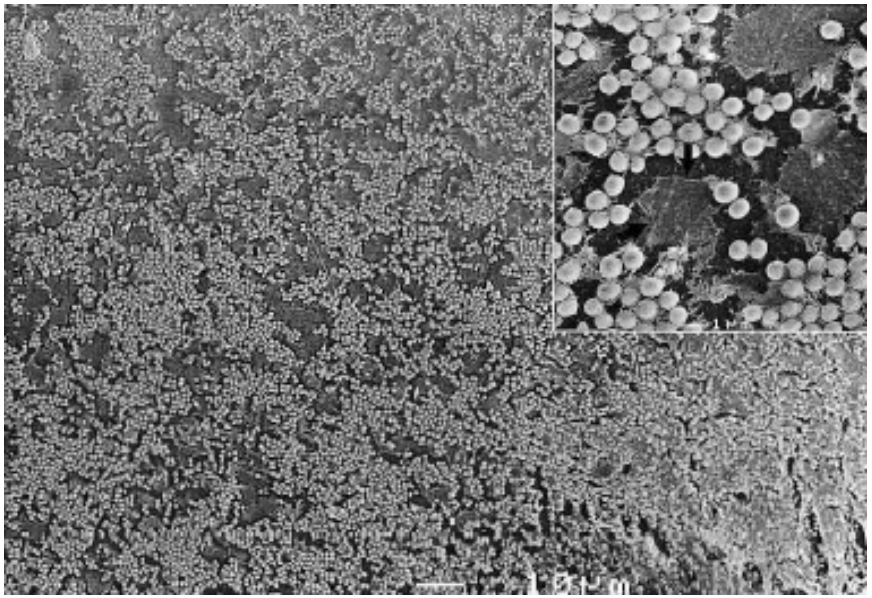
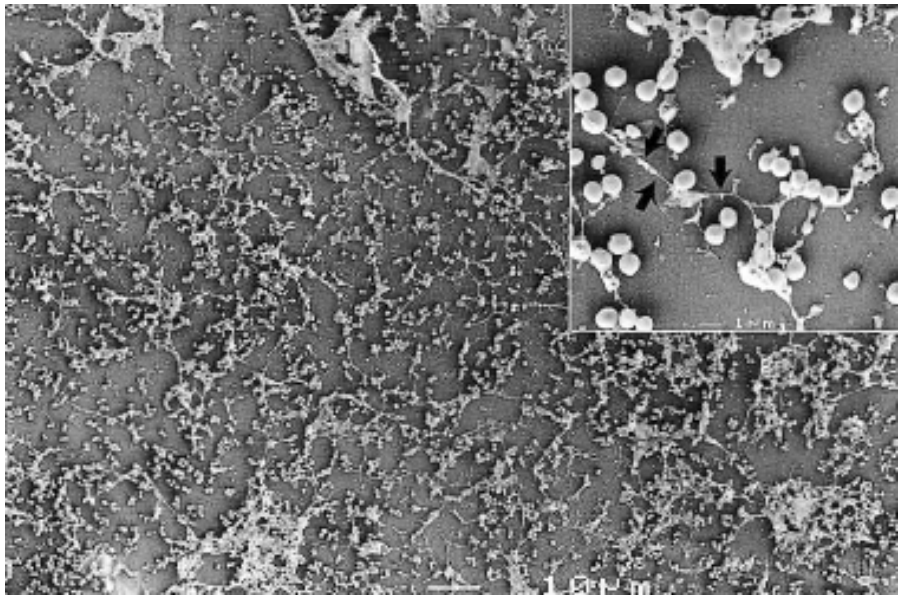
**Unloaded bone cement**



**Gentamicin-loaded bone cement**



Surface rugueuse du ciment = excellent support d'adhésion *Kendall, J Arthroplasty 1995*

# Ciment AB: Emergence de résistance

## Biomaterial-associated infection of gentamicin-loaded PMMA beads

***Neut, JAC 2001***

Culture de billes gentamicine (30 billes de 4.5mg gentamicine) de 20 patients avec infection prothèse

Comparaison **culture standard** (4/20 positives) vs **culture prolongée** sur milieux enrichis (18/20 positives)

**Table I.** Bacteria isolated from excised tissue of patients with a suspected infection of an orthopaedic prosthesis by routine hospital culture and from gentamicin-loaded PMMA beads by an extensive laboratory procedure

| | | Routine hospital results | | Extended procedure results | |
|---|---|---|---|---|---|
| Patient | Prosthesis | tissue I | tissue II | beads I | beads II |
| 1 | hip | no growth | no second insertion | CNS | no second insertion |
| 2 | knee | *Peptostreptococcus magnus* | no second insertion | anaerobe | no second insertion |
| 3 | knee | no growth | no growth | CNS | CNS |
| 4 | hip | no growth | no growth | *P. aeruginosa* | *P. aeruginosa* |
| | | | | | CNS |
| 5 | hip | no growth | no growth | *Pseudomonas diminuta* | no growth |
| | | | | *S. maltophilia* | |
| 6 | hip | not tested[a] | no second insertion | *S. aureus* | no second insertion |
| | | | | CNS | |
| 7 | knee | not tested[a] | no second insertion | *Pseudomonas* | no second insertion |
| 8 | hip | no growth | no second insertion | CNS | no second insertion |
| | | | | *Pseudomonas* | |
| 9 | shoulder | no growth | no second insertion | no growth | no second insertion |
| 10 | hip | no growth | no second insertion | CNS | no second insertion |
| | | | | *S. aureus* | |
| 11 | hip | no growth | no second insertion | CNS | no second insertion |
| 12 | hip | no growth | no growth | CNS | no growth |
| 13 | hip | no growth | no second insertion | no growth | no second insertion |
| 14 | hip | *P. aeruginosa* | no second insertion | *P. aeruginosa* | no second insertion |
| | | CNS | | CNS | |
| 15 | hip | *Enterococcus faecalis* | no second insertion | CNS (2×) | no second insertion |
| 16 | hip | no growth | no second insertion | *C. acidovorans* | no second insertion |
| 17 | hip | no growth | no second insertion | *Enterococcus* | no second insertion |
| 18 | knee | no growth | no second insertion | CNS | no second insertion |
| 19 | hip | not tested[a] | no second insertion | CNS | no second insertion |
| 20 | hip | no growth | no second insertion | CNS | no second insertion |
| | | | | *S. sanguinis* | |

Samples taken after the first insertion of a chain of gentamicin-loaded PMMA beads are indicated I, while samples taken from patients requiring a second insertion are denoted II.

[a]No tissue samples taken based on a per-operative visual inspection of the wound area by the orthopaedic surgeon, concluding that the patient was free of infection.

**Table II.** MICs for bacteria isolated from the gentamicin-loaded PMMA beads retrieved from patients with a suspected infection of an orthopaedic prosthesis, obtained by an extensive laboratory culture procedure

| Patient | Beads I | MIC (mg/L) | Beads II | MIC (mg/L) |
|---|---|---|---|---|
| 1 | CNS | >256 | no second insertion | |
| 2 | anaerobe | not tested[a] | no second insertion | |
| 3 | CNS | 0.75 | CNS | 1.0 |
| 4 | *P. aeruginosa* | 2 | *P. aeruginosa* | 4 |
| | | | CNS | >256 |
| 5 | *P. diminuta* | 96[b] | no growth | |
| | *S. maltophilia* | >256[b] | | |
| 6 | *S. aureus* | 12[b] | no second insertion | |
| | CNS | 0.75 | | |
| 7 | *Pseudomonas* | 24 | no second insertion | |
| 8 | CNS | 0.50 | no second insertion | |
| | *Pseudomonas* | 4 | | |
| 9 | no growth | | no second insertion | |
| 10 | CNS | >256 | no second insertion | |
| | *S. aureus* | 0.75 | | |
| 11 | CNS | >256 | no second insertion | |
| 12 | CNS | 0.25 | no growth | |
| 13 | no growth | | no second insertion | |
| 14 | *P. aeruginosa* | 6 | no second insertion | |
| | CNS | >256 | | |
| 15 | CNS | >256 | no second insertion | |
| | CNS | 32[b] | | |
| 16 | *C. acidovorans* | 24 | no second insertion | |
| 17 | *Enterococcus* | 1.5 | no second insertion | |
| 18 | CNS | 0.38 | no second insertion | |
| 19 | CNS | >256 | no second insertion | |
| 20 | CNS | >256 | no second insertion | |
| | *S. sanguinis* | >256[b] | | |

Samples taken after the first insertion of chains are indicated I, while samples taken from patients requiring a second insertion are denoted II.

[a]Anaerobes are resistant to gentamicin.

[b]Development of resistant sub-populations.

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*Van de Belt, Acta Orthop Scand 2000*

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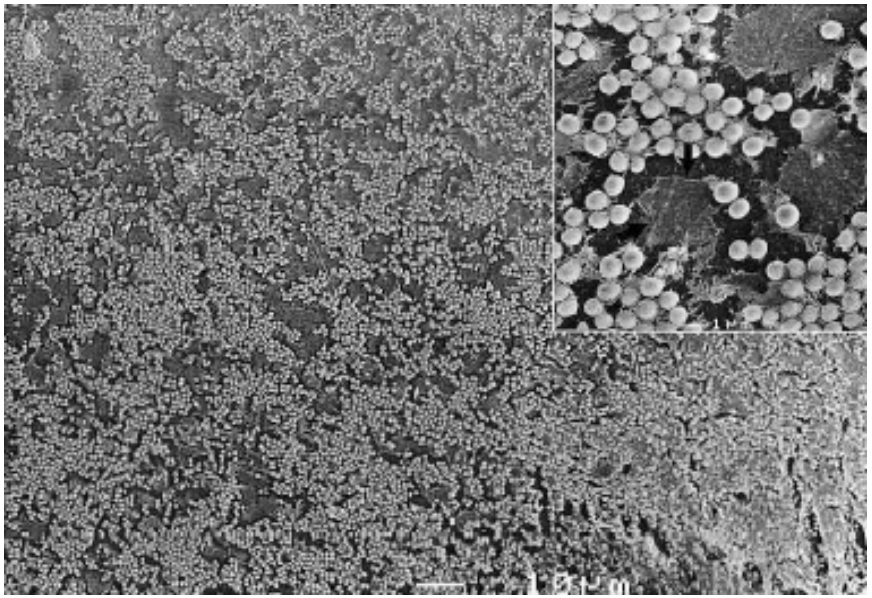

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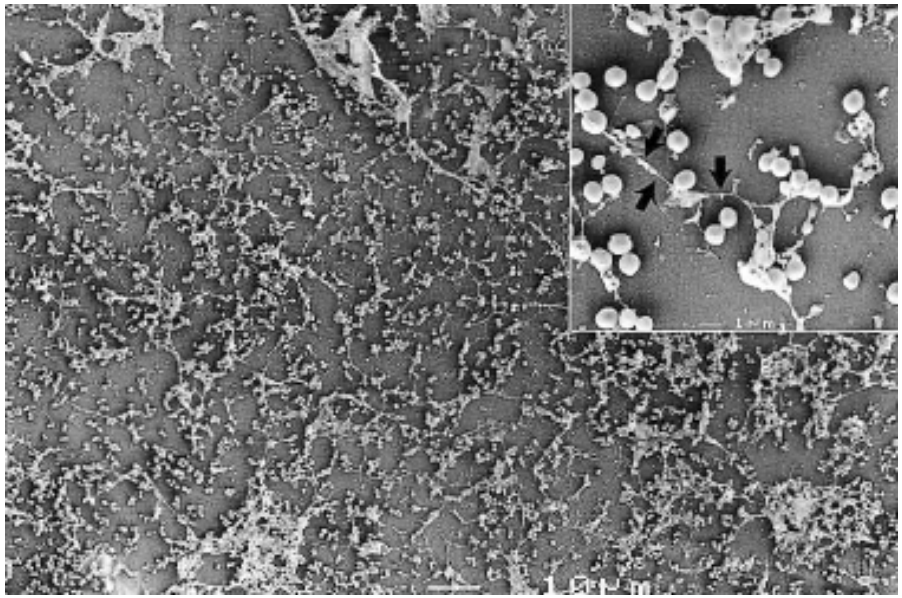

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| 4 | *P. aeruginosa* | 2 | *P. aeruginosa* | 4 |
| | | | CNS | >256 |
| 5 | *P. diminuta* | 96[b] | no growth | |
| | *S. maltophilia* | >256[b] | | |
| 6 | *S. aureus* | 12[b] | no second insertion | |
| | CNS | 0.75 | | |
| 7 | *Pseudomonas* | 24 | no second insertion | |
| 8 | CNS | 0.50 | no second insertion | |
| | *Pseudomonas* | 4 | | |
| 9 | no growth | | no second insertion | |
| 10 | CNS | >256 | no second insertion | |
| | *S. aureus* | 0.75 | | |
| 11 | CNS | >256 | no second insertion | |
| 12 | CNS | 0.25 | no growth | |
| 13 | no growth | | no second insertion | |
| 14 | *P. aeruginosa* | 6 | no second insertion | |
| | CNS | >256 | | |
| 15 | CNS | >256 | no second insertion | |
| | CNS | 32[b] | | |
| 16 | *C. acidovorans* | 24 | no second insertion | |
| 17 | *Enterococcus* | 1.5 | no second insertion | |
| 18 | CNS | 0.38 | no second insertion | |
| 19 | CNS | >256 | no second insertion | |
| 20 | CNS | >256 | no second insertion | |
| | *S. sanguinis* | >256[b] | | |

Samples taken after the first insertion of chains are indicated I, while samples taken from patients requiring a second insertion are denoted II.

[a]Anaerobes are resistant to gentamicin.

[b]Development of resistant sub-populations.

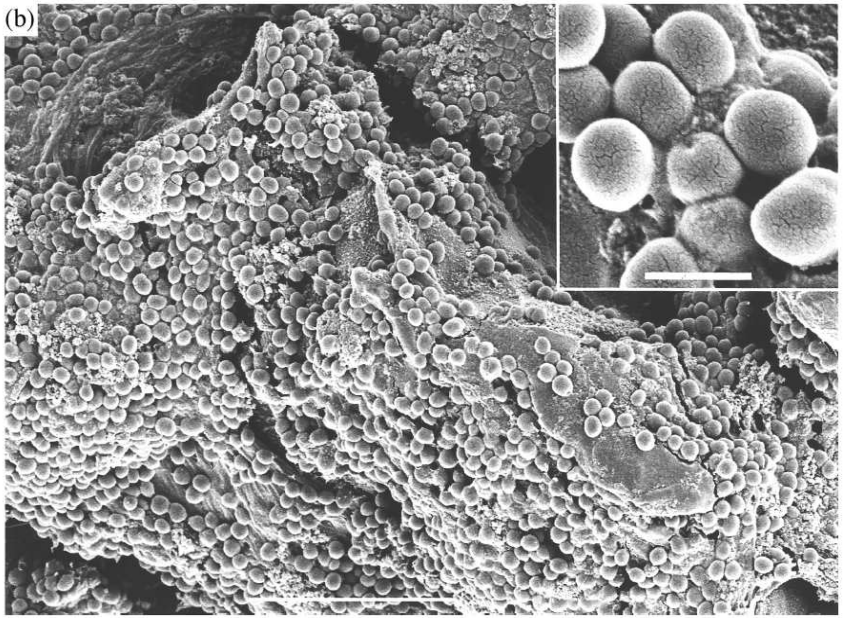
# Ciment AB: Emergence de résistance

Biomaterial-associated infection of gentamicin-loaded PMMA beads

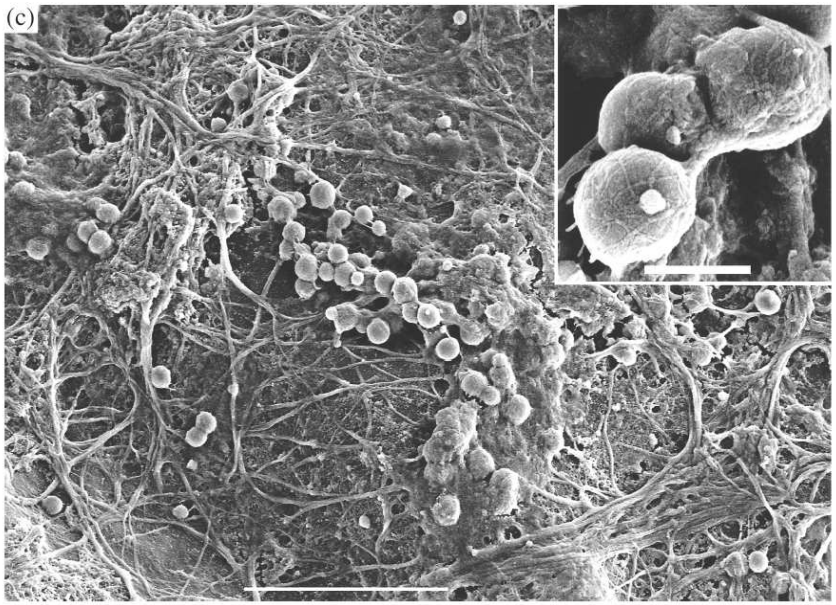
*Neut, JAC 2001*

Mise en culture de billes de gentamicine (30 billes de 4.5mg gentamicine) de 20 patients pris en charge pour infection prothèse.

Comparaison de culture standard vs culture prolongée sur milieux enrichis




Patient 11: culture prolongée avec SCN




Patient 14: culture prolongée avec SCN et *P. aeruginosa*

# Ciment AB: ETUDES CLINIQUES

## Traitement préventif PTH

| Références | Type d'étude | Résultats |
|---|---|---|
| Joseffson<br>Clin Orthop<br>Rel Res 1993 | Etude randomisée suédoise 1976-1978 | 2 ans: ABP 13 IP (1.6%), CCT 3 IP (0.4%) p<0.05<br>5 ans: ABP 16 IP (1.9%), CCT 7 IP (0.8%) p<0.05 |
| | AB prophylaxie (ABP, n=835) vs ciment genta (0.5g) (CGT,n=853) | 10 ans: ABP 16 IP (1.9%), CCT 9 IP (1%) NS |
| Engesaeter<br>Acta Orthop<br>Scan 2003 | Registre norwégien 1987-2001<br>N=22170 | IPTH 0.5% (n=102)<br>Sans ciment AB (CAB) 1.4 x plus reprises (p=0.001),<br>1.8 x plus reprises pour infection (p =0.01) |

# Ciment AB: ETUDES CLINIQUES

## Traitement préventif PTG

| Références | Type d'étude | Résultats |
|---|---|---|
| Jämsen<br>JBJS 2009 | Registre finlandais<br>N = 43149<br>PTG (première, révision) | IPTG 0.9% (n=387)<br>Sans CAB : 1.35 x plus reprises pour infection vs CAB + ABP |
| Namba<br>JBJS 2013 | Analyse FdR d'infection prothèse<br>Cohorte PTG (première), 2001-2009<br>N= 56216, 0.72% (n=404 IP)<br>ABP 93%, CAB 12%, irrigation AB 15% | Analyse multi-variée:<br>BMI ≥ 35 (HR 1.47), diabète (HR 1.28), sexe masculin (HR 1.89), score ASA ≥ 3 (HR 1.65), osteonécrose (HR 3.65), arthrose post-traumatique (HR 3.23), ciment AB (HR 1.53), irrigation AB (HR 0.67) |
| Hinarejos<br>JBJS 2013 | Etude prospective randomisée<br>N=2984 PTG (première)<br>Groupe ciment sans AB (n=1465)<br>Groupe ciment érythro/colistin (n= 1483) | Suivi ≥ 12 mois:<br>Pas différence entre 2 groupes (IP 1.4% sans AB vs 1.35% avec AB) |

# Ciment AB: ETUDES CLINIQUES

## Traitement curatif

**Surgical procedures in the treatment of 784 infected THAs reported to the Norwegian Arthroplasty Register**

Best survival with 2-stage exchange revision, but also good results with debridement and retention of the fixed implant

***Acta Orthop 2011***

Lars B Engesæter[1, 2], Håvard Dale[1], Jan C Schrama[1], Geir Hallan[1], and Stein Atle Lie[1, 2]

**Registre norvégien PTH de 1987-2009**

- date opératoire, indication
- type prothèse, durée intervention?
- type de fixation(+/- ciment, +/- AB)

906 (0.7%) infections de prothèse (IP)

**Utilisation de ciment aux AB**

- 252 avec ciment aux AB
- 201 sans ciment

**Risque de reprise non différent**

- toute cause RR 1.3 [0.8-2]
- pour infection RR 0.98 [0.5-1.9]

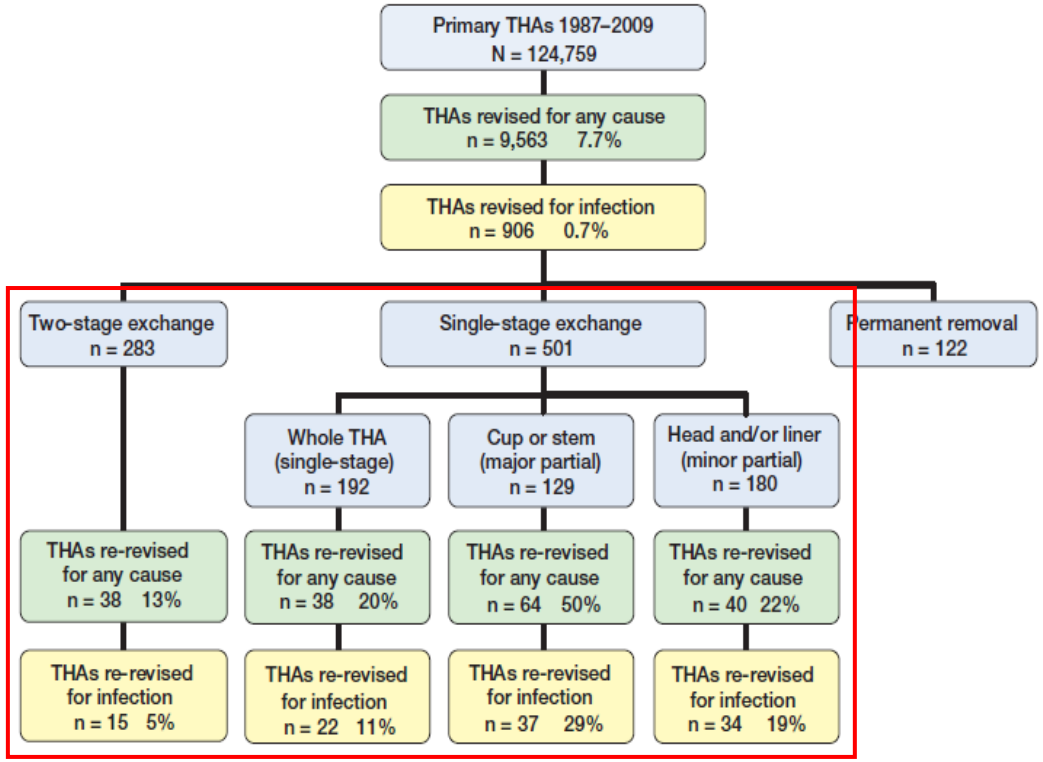



Figure 1. Flow chart showing the entire THA cohort and the different subgroups of surgical revision procedures (number and percentage) for revisions performed for any cause and due to infection.

# Ciment AB: ETUDES CLINIQUES

## Traitement curatif

Choice and Doses of Antibacterial Agents for Cement Spacers in Treatment of Prosthetic Joint Infections: Review of Published Studies

D. Ianikov,[1] H. Demian,[2] D. Rubin,[3] J. Alexander,[1] and S. Nambiar[1]

***CID 2012***

- **Objectif**
  - Evaluer qualité scientifique du choix, posologie ciment AB dans traitement des infections de prothèse (IP) avec changement en 2 temps
- **Méthodes**
  - Revue littérature 1988-2011
  - Critères d'inclusion: posologie AB calculable/40g ciment, même composition de ciment pour tous patients, suivi après repose ≥ 24 mois
  - Objectif principal: taux d'éradication d'IP à 2 ans
- **Résultats**
  - 20 études, 836 IP (71% PTG, 29% PTH)
  - Une seule étude randomisée (IPTH): spacer vanco (1g/40g) vs pas de spacer
    *Cabrita, Clinics 2007*
  - Nombreuses études exclues
    - hétérogénéité dans composition du spacer
    - suivi insuffisant

# Choice and Doses of Antibacterial Agents for Cement Spacers in Treatment of Prosthetic Joint Infections: Review of Published Studies

D. Iarikov,[1] H. Demian,[2] D. Rubin,[3] J. Alexander,[1] and S. Nambiar[1]

## Résultats

| Study by Arthroplasty Site | Study Period | Patients, No./ Joints, No. | Spacer Antibiotic Content (Dose, g/40 g Cement) | Infection Eradication Rate[a] | | Deaths[b] |
|---|---|---|---|---|---|---|
| | | | | By Review | As Reported by Authors | |
| Knee | | | | | | |
| [43] | Not reported | 12/12 | Tobramycin (4.8) + vancomycin (4) | 12/12 (100) | 12/12 (100) | 0 |
| [17][c] | 1995–2002 | 29/31 | Tobramycin (4.6) + vancomycin (4) | 25/31 (81) | 29/31 (93) | 0 |
| [15][d] | 1998–2005 | 102/102 | Tobramycin (3.6) + vancomycin (4) | 47/102 (46) | 70/96 (73) | 0 |
| [20] | 1986–1994 | 48/48 | Tobramycin (3.6) + vancomycin (2) | 43/48 (90) | 44/48 (92) | 0 |
| [13][d] | 1997–1999 | 58/58 | Tobramycin (3.6) + vancomycin (1.5) | 48/58 (83) | 45/47 (96) | NA[e] |
| [44] | 1998–2001 | 24/24 | Tobramycin (2.4) + vancomycin (1) | 22/24 (92) | 22/24 (92) | 0 |
| [45] | 1996–2001 | 28/28 | Tobramycin (1.2) or gentamicin (1) + vancomycin (1) | 25/28 (89) | 25/28 (89) | 0 |
| [46] | 2000–2005 | 36/36 | Piperacillin-tazobactam (4.5) + vancomycin (2) + erythromycin (1) | 32/36 (89) | 32/36 (89) | 0 |
| [18] | 1989–2001 | 50/50 | Tobramycin (4.8) | 44/50 (88) | 44/50 (88) | NA |
| [22] | 1994–2002 | 44/44 | Tobramycin (4.8) | 43/44 (98) | 43/44 (98) | 0 |
| [14][d] | 1986–1999 | 40/40 | Tobramycin (1.2) | 36/40 (90) | 36/40 (90) | 0 |
| [19] | 1989–1993 | 69/69 | Tobramycin (1) | 60/69 (87) | 61/69 (88) | 0 |
| [47][f] | 1998–2003 | 48/48 | Vancomycin (1) | 30/48 (63) | 42/48 (88) | 0 |
| Hip | | | | | | |
| [17][c] | 1995–2002 | 16/23 | Tobramycin (4.6) + vancomycin (4) | 18/23 (78) | 22/23 (96) | 0 |
| [48] | Not reported | 12/12 | Tobramycin (3.6) + vancomycin (1) | 12/12 (100) | 12/12 (100) | 0 |
| [12][d] | 1998–2001 | 22/22 | Tobramycin (2.4) + vancomycin (1) | 20/22 (90) | 20/20 (100) | 2 (9) |
| [10][d] | 1993–1997 | 24/24 | Gentamicin (1) + vancomycin (1) + cefotaxime (1) | 21/24 (88) | 21/22 (95) | 2 (8) |
| [16][d,f] | 1998–2003 | 43/44 | Gentamicin (0.25) + vancomycin (2) | 35/44 (80) | 38/41 (93) | 3 (7) |
| [11][d] | 1991–2001 | 42/42 | Tobramycin (4.8) | 26/42 (62) | 26/27 (96) | 8 (19) |
| [9][g] | 1996–2003 | 38/38 | Vancomycin (1) | 32/38 (84) | 34/38 (89) | 2 (5) |
| [23][h] | 2001–2006 | 40/40 | Gentamicin (0.76) | 38/40 (95) | 39/40 (97.5) | 0 |

Choice and Doses of Antibacterial Agents for Cement Spacers in Treatment of Prosthetic Joint Infections: Review of Published Studies

D. Iarikov,[1] H. Demian,[2] D. Rubin,[3] J. Alexander,[1] and S. Nambiar[1]

# Discussion

- Pas d'association entre composition/posologie spacer aux AB et l'évolution des patients
- Evolution favorable *[Cabrita 2007]* malgré résistance germes (BGN 31.5%).
- Pas d'étude randomisée avec spacer +/- antibiotique ou compositions variables
- Différence dans les ciments et composition
- Résistance des staphylocoques aux aminosides élevée (41-74%)

## Conclusion

- Qualité scientifique des données insuffisante pour recommander l'utilisation de spacer aux AB
- Recommandations reposent sur les avis d'expert et études *in vitro*

# Ciment AB: ETUDES CLINIQUES

## Traitement curatif

**One-stage exchange arthroplasty for chronic prosthetic hip infection: results of a large prospective cohort study**
***Zeller et al, JBJS (sous presse)***

Étude prospective (11/2002-03/2009)
152 IPTH traitées par un temps

**Pas d'antibiothérapie locale**
**Prothèses non cimentées** (45%)

Antibiothérapie par voie générale
- durée (médiane)
  - totale 90 jours [43-135]
  - IV 42 jours [28-86]

**Suivi** 39 [24-86] mois

Rechutes très rares 2/152 (1.3%)
Récidives peu fréquentes 8/152 (5%)

| **Pathogènes** | **N (%)** |
|---|---|
| ***Staphylococcus*** | **84 (54%)** |
| MS | 36 (23%) |
| MR | 49 (31%) |
| ***S. aureus*** | **23 (15%)** |
| MS | 17 |
| MR/GI | 5/1 |
| ***S. epidermidis*** | **40 (25%)** |
| MS | 6 |
| MR/GI | 22/12 |
| Autres staphylocoques | 13 (8%) |
| ***Streptococcus*** | **20 (13%)** |
| Beta-hemolytic | 10 |
| *Streptococcus viridans* | 10 |
| ***Enterococcus faecalis*** | **4** |
| **Bacilles à Gram négatif** | **16 (10%)** |
| **Anaérobies Gram +** | **18 (11%)** |
| **Infection pluri-microbienne** | **11 (7%)** |
| **Autres germes** | **3** |
| **Absence documentation** | **1** |

# Ciment AB: TOXICITE

**Menge et al. Acute kidney injury after placement of an antibiotic-impregnated cement spacer during revision total knee arthrplasty** ***J Arthroplasty 2012***

• **Objectifs**: Incidence et facteurs prédictifs d'insuffisance rénale aiguë après mise en place spacer AB pour le traitement d'infection de PTG

IRA: augmentation >50% créatinine de base et >14mg/L dans les 90 jours post-opératoires.

Etude rétrospective sur 84 patients

• **Résultats**: Incidence 17% [95%CI 10-26].

IRA associé à

- dose tobramycine > 4.8g, OR 5.87 [95%CI 1.43-24.19]

- dose tobramycine (variable linéaire) OR 1.24 [95%CI 1.00-1.52] pour chaque 1g supplémentaire

# Ciment AB: TOXICITE

**Luu et al. Two-stage arthroplasty for prosthetic joint infection. A systematic review of acute kidney injury, systemic toxicity and infection control**
***J Arthroplasty 2013***

Revue de la littérature de 1989-2012.

• **Objectifs**: Evaluer bénéfice-risque du spacer AB lors changement en 2 temps. Incidence d'insuffisance rénale et récidive d'infection de prothèse.

• **Résultats**: 10 études observationnelles, 544 patients.
Hétérogénéité du type spacer et AB utilisés. Tobramycine, gentamicine (80%) +/- vancomycine (60%) le plus souvent utilisés. Durée spacer (4/10): 6 à 17 semaines.

**Incidence de l'IRA** (4 études): 26/544 patients (**4.8% ;** 2-17% selon études et définitions). **Plus élevée** que décrit précédemment.
Incidence récidive d'infection 11%.

• **Conclusion:** Rapport bénéfice-risque plutôt en faveur spacer AB.
MAIS: IRA sous-estimée ? Difficultés d'interprétation des résultats, car hétérogénéité des définitions, spacer, suivi, étude rétrospectives…

# Ciment AB: TOXICITE

## Cas cliniques: Insuffisance rénale aiguë sévère (5 cas)

*Van Raaij, J Arthroplasty 2002*

*Curtis, Pharmacotherapy 2005*

*Patrick, Ann Pharmacother 2006*

*Dovas, Clin Nephrol 2008*

*McGlothan KR, Tenn Med 2012*

Spacer avec tobramycine (3), gentamicine (1), vancomycine (1)

Posologie: genta/tobra 0.5-3.6g/40g; vancomycine 2-3g/40g

Apparition de l'IRA: immédiate chez 3, décalée de 1.5-5 mois chez 2 patients

4/5 patients avec concentration sérique d'aminosides 2-5.5µg/ml

3 patients dialysés

Régression de l'insuffisance rénale après ablation du spacer

# Les ciments AB sont-ils utiles en chirurgie orthopédique prothétique? NON

## Traitement préventif

- Utilisation large à faible posologie: conséquences ?
- Risques
  - Effet mécanique: non observé
  - Risque toxicité, allergie: non observé
  - Risque résistance aux AB ?
  - Coût ?

- Diminution de l'incidence des infections prothèse ?
- Effet sur long terme: efficacité, résistance ?

- Recommandations et utilisations (USA 10%, Scandinavie, GB > 90%) variables selon pays

- Développement de prothèses non cimentées

# Les ciments AB sont-ils utiles en chirurgie orthopédique prothétique? NON

## Traitement curatif

- Efficacité difficile à apprécier
  - Aucune étude randomisée
  - Hétérogénéité majeure dans les études et les pratiques
  - Efficacité de la prise en charge en absence d'antibiothérapie locale

- Courte durée d'efficacité (< 2 semaines)
- Spacer = corps étranger avec risque colonisation et formation du biofilm
- Risque d'acquisition de résistance

- Difficultés pratiques
  - Antibiothérapie active: diagnostic microbiologique pré-opératoire
  - Modifications des propriétés physico-chimiques du ciment à forte posologie
  - Toxicité, allergie
  - Risque de cultures faussement stériles en cas de reprise

- Développement de prothèses non cimentées

- Recommandations variables selon pays

# Diagnosis and Management of Prosthetic Joint Infection: Clinical Practice Guidelines by the Infectious Diseases Society of America[a]

**Douglas R. Osmon,[1] Elie F. Berbari,[1] Anthony R. Berendt,[2] Daniel Lew,[3] Werner Zimmerli,[4] James M. Steckelberg,[1] Nalini Rao,[5,6] Arlen Hanssen,[7] and Walter R. Wilson[1]**

[1]Division of Infectious Diseases, Mayo Clinic College of Medicine, Rochester, Minnesota; [2]Bone Infection Unit, Nuffield Orthopaedic Centre, Oxford University Hospitals NHS Trust, United Kingdom; [3]Division of Infectious Diseases, Department of Internal Medicine, University of Geneva Hospitals, [4]Basel University Medical Clinic, Liestal, Switzerland; [5]Division of Infectious Diseases, Department of Medicine, and [6]Department of Orthopaedic Surgery, University of Pittsburgh School of Medicine, Pennsylvania, and [7]Department of Orthopedics, Mayo Clinic College of Medicine, Rochester, Minnesota

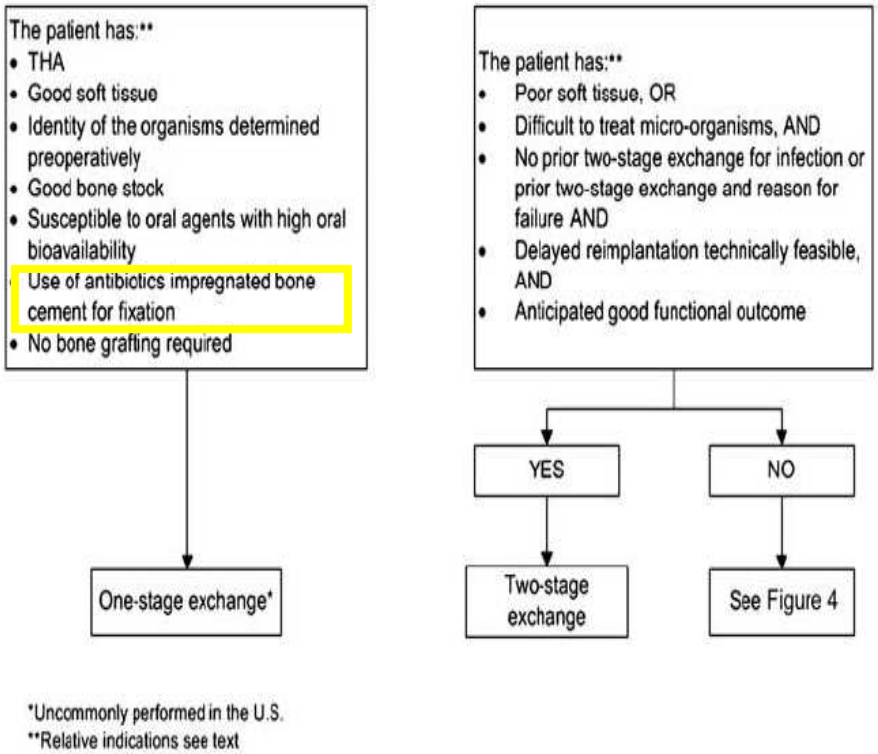



**Figure 3.** Management of prosthetic joint infection—removal of prosthesis. Abbreviation: THA, total hip arthroplasty.

*CID 2013*

Local AB impregnated cement and devices are commonly used…either premixed or mixed…by the surgeon.

The clinicians should be aware of the potential for systemic toxicity of local antimicrobial delivery, although this rarely occurs.

Some panel members do not recommend spacers for MRSA infection…, as they believe that the use of spacers in these settings may be detrimental to the eradication of infection. Reports of successful use of spacers for MRSA PJI have been published.

The use of AB impregnated cement and spacers has not been evaluated in randomized controlled trials.

## 3.3.1 Quelle est la place de l'antibiothérapie locale ?

3.3.1.1.2 Ces ciments ne seront donc utilisés que de façon transitoire sous 2 formes :

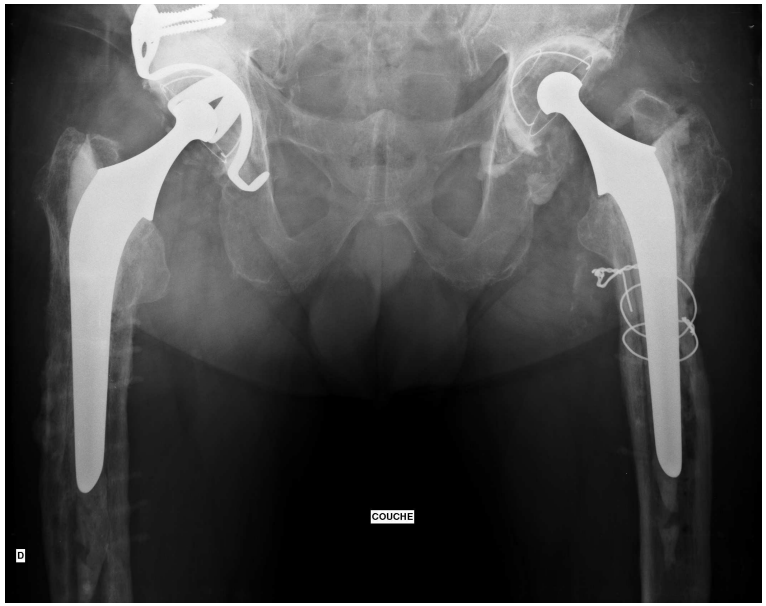
- les billes de ciment servant à combler une cavité. Imprégnées d'antibiotiques, elles vont pouvoir en assurer une diffusion locale pendant les premières semaines. Elles seront secondairement retirées [206, 207].

- l'entretoise ou espaceur au ciment imprégné d'antibiotiques ayant pour but d'une part de maintenir l'espace après la dépose de l'implant et d'autre part de diffuser une antibiothérapie locale grâce à des doses élevées d'antibiotiques.

Ces ciments ne doivent en aucun cas dispenser de la prescription d'une antibiothérapie par voie générale.

3.3.1.2.2 Les antibiotiques utilisés dans le ciment doivent être hydrosolubles, résister à la température élevée, avoir le moins d'effet possible sur les propriétés mécaniques du ciment et être actifs vis-à-vis de la bactérie identifiée lors des prélèvements. Ce sont actuellement les aminosides, la vancomycine, la clindamycine [209].

# Ciment AB: Emergence de résistance




**Hip arthroplasty infection with heterogeneous vancomycin-resistant Staphylococcus aureus**

VALÉRIE ZELLER[1], MARIE-DOMINIQUE KITZIS[2], WILFRID GRAFF[1], PATRICK MAMOUDY[1] & NICOLE DESPLACES[1]

*From the [1]Department of Orthopaedic Surgery, Groupe Hospitalier Diaconesses-Croix Saint-Simon, and [2]Department of Microbiology, Hôpital Saint-Joseph, Paris, France*

Ciment vancomycine

Teicoplanine IV 18 mois

***Scan J Inf Dis 2006***

**Hétéro GISA**

**CMI vanco = 4 to 16 µg/ml**

**CMI teicoplanine = 24 mg/ml**

Table II. Vancomycin and teicoplanin concentrations in serum (µg/ml) and intra-operative (6 September 2002) samples (µg/g).

| Antibiotic | Serum | Capsule | Acetabulum | Proximal femur | Distal femur | Bone adjacent to cement | Cement |
|---|---|---|---|---|---|---|---|
| Vancomycin | <2 | 6.1 | 67 | 289 | 2088 | 10.2 | 1577 and 75 |
| Teicoplanin | 31 | 31 | 30 | 3.9 | <4 | ND | |

Cultures of the specimens grew heterogeneous vancomycin-resistant S. aureus (MIC: vancomycin, 8–12 µg/ml; teicoplanin, 24 µg/ml). At that time, the patient was receiving i.v. teicoplanin and his second left hip prosthesis had been implanted 14 months earlier with vancomycin-loaded cement.

# TOXICITE

Choice and Doses of Antibacterial Agents for Cement Spacers in Treatment of Prosthetic Joint Infections: Review of Published Studies

D. Iarikov,[1] H. Demian,[2] D. Rubin,[3] J. Alexander,[1] and S. Nambiar[1]

Conclusion difficile en l'absence d'études comparatives

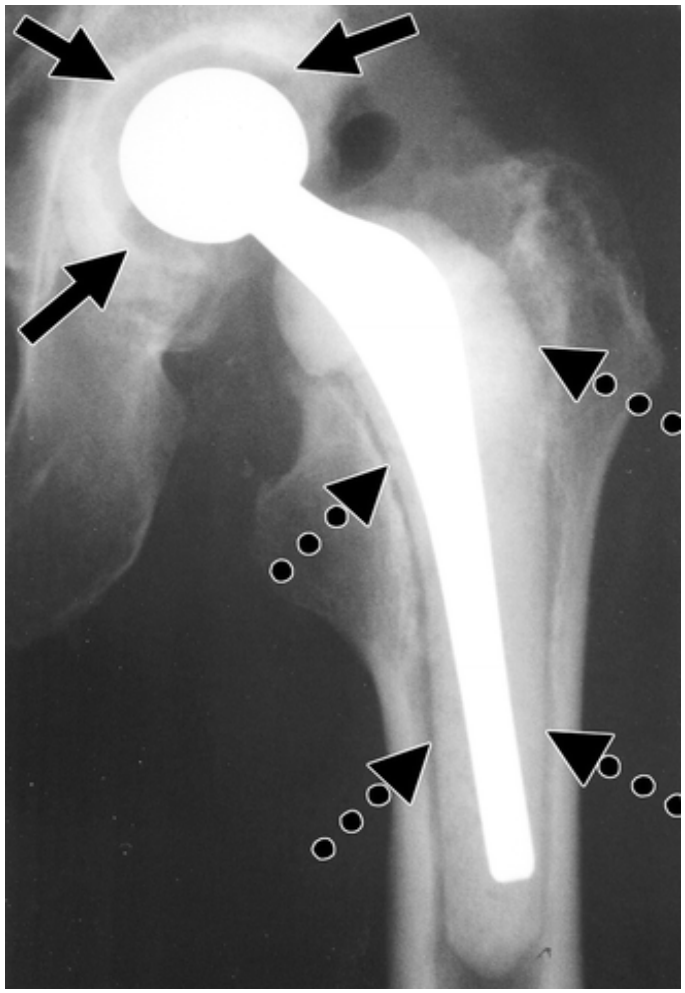
**TOXICITÉ RÉNALE RARE**

5 des 20 études incluses [9, 10, 16-18]

- 5 études supplémentaires [28-32]

| Study | Patients, No./ Joints, No. | ACS Composition (Dose, g/40 g cement) | Patients With Systemic Toxicity, No. (%) | | |
|---|---|---|---|---|---|
| | | | Renal | Vestibular | Liver Dysfunction and Bone Marrow Suppression |
| [9] | 38/38 hips | Vancomycin (1) | 0 | NC | 0 |
| [17] | 44/54 hips | Tobramycin (4.6) + vancomycin (4) | 0 | 0 | NC |
| [18] | 50/50 knees | Tobramycin (4.8) | 0 | 1 (2) | NC |
| [10] | 24/24 hips | Gentamicin (1) + vancomycin (1) + cefotaxime (1) | NC | NC | 4 (17) |
| [16] | 43/44 hips | Gentamicin (0.25) + vancomycin (2) | 2 (5) | 0 | 0 |
| [28] | 34/36 knees | Gentamicin (4.8) + vancomycin (4) | 0 | 0 | 0 |
| [29] | 42/42 hips | Liquid gentamicin (480 mg; 24 patients); liquid gentamicin (480 mg) and vancomycin (3.0; 18 patients) | 0 | NC | NC |
| [30] | 110/115 knees | Not specified | 2 (2) | 0 | 0 |
| [31] | 82/88 hips | Gentamicin (0.5) + vancomycin (2) | 5 (6) | 0 | 0 |
| [32] | 10/10 hips | vancomycin (2–3) | 1 (10%) | NC | 0 |

Abbreviations: ACS, antibacterial cement spacer; NC, no specific comments provided.



PROSTALAC: prosthesis with antibiotic loaded cement

*Gee, AJR 2003*

# ANTIBIOTIC-LOADED ACRYLIC CEMENT

JBJS 1977

R. A. Elson, A. E. Jephcott, Sheffield, England, D. B. McGechie, Hong Kong
and D. Verettas, Sheffield, England

**Laboratory experiments and clinical investigations have confirmed the various claims made originally by Buchholz and Engelbrecht (1970) that antibiotic-loaded acrylic cement releases the antibiotic into the surroundings in useful concentrations. Palacos R cement released higher concentrations than CMW, Simplex and Sulfix brands of cement and over longer periods. Concentrations of gentamycin and fucidin were sufficient to penetrate dead cortical bone. These conclusions need to be assessed with animal studies, mechanical testing and clinical results before the ideal place of antibiotic-loaded acrylic cement is established.**

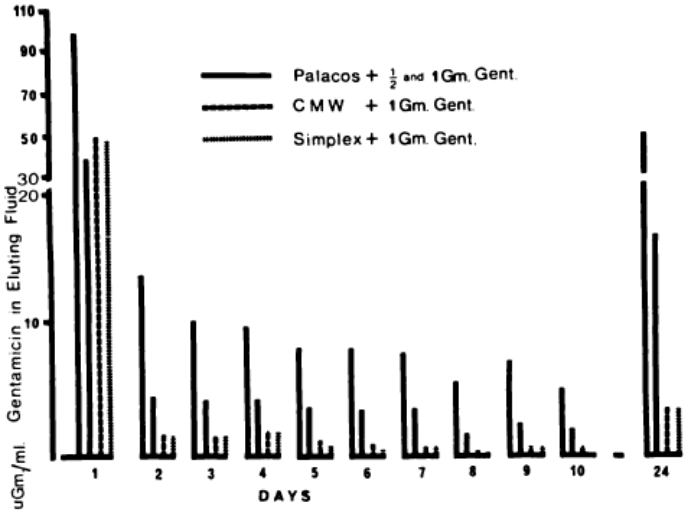



FIG. 2

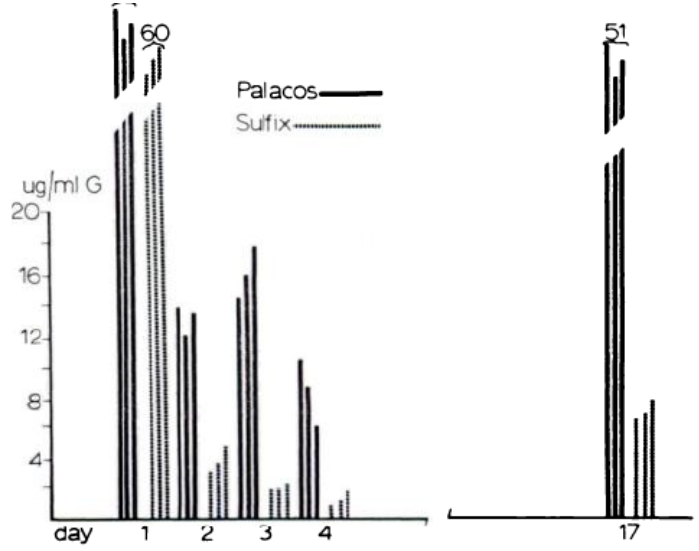



FIG. 3

Concentrations of gentamicin eluted from blocks of gentamicin-loaded acrylic cements. Figure 2—Comparison of Palacos-R containing 1·0 gram and 0·5 gram per 40-gram powdered polymer, before curing, with CMW and Simplex containing 1·0 gram. Figure 3—Comparison of Palacos-R with Sulfix. From the fourth consecutive day, the concentrations eluted are low, but after leaving the pots undisturbed for about thirteen days, significant concentrations can be measured.

# MANAGEMENT OF DEEP INFECTION OF TOTAL HIP REPLACEMENT

JBJS 1981

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*From the Endo-Klinik, Hamburg*

**Exchange operation is recommended as the treatment of choice for most deep infections involving a total hip replacement. This revision arthroplasty comprises, in one stage, excision of soft tissue, removal of implant and cement, replacement with an appropriate implant using Palacos R acrylic cement loaded with an appropriate antibiotic and, more recently, systemic antibiotics. During our first 10 years without systemic antibiotics we have achieved an overall 77 per cent success rate from a first attempt in 583 patients and a 90 per cent success rate after subsequent exchange procedures. Morbidity is significant but acceptable. Success is defined as control of infection, no loosening, and useful function. The factors associated with failures include, in particular, specific infections (*Pseudomonas* group, *Streptococcus* group D, *Proteus* group, and *Escherichia coli*), delay in operation and inadequate antibiotic dosage in the cement.**

**Table A2.** Antibiotic substances which have been added to methylmethacrylate bone cement

| | | | |
|---|---|---|---|
| Amikacin * | Cephalothin * | Erythromycin † | Oxacillin * |
| Ampicillin * | Chloramphenicol † | Fucidin † | Penicillin † |
| Azlocillin * | Clindamycin * | Gentamicin * | Streptomycin * |
| Bacitracin † | Epicillin * | Lincomycin * | Tobramycin * |
| Cefoxitin * | | | |

* in current use
† not now advised

**Table A3.** Examples of antibiotics and doses (expressed as weight of antibiotic base) added to 40 grams of polymer powder before addition to the liquid monomer

(a) For a clinical infection in which no organism has been cultured:

| | | |
|---|---|---|
| gentamicin | 1.0 gram | |
| cephalothin | 2.0 grams | elution much shorter lived but highly effective in initial postoperative period |
| oxacillin | 0.5 gram | |

(b) For a known infection in which organism has been cultured and cross-antibiotic sensitivities have been assessed, choice of antibiotics and dosage is a balance between the good chance of controlling the infection and the adverse weakening effect. Common combinations are:

*Staphylococcus aureus:*

| | |
|---|---|
| gentamicin | 1.0 gram |
| lincomycin | 2.0–4.0 grams |

*Peptococcus* group:

| | |
|---|---|
| gentamicin | 1.0 gram |
| ampicillin | 2.0–4.0 grams |

*Corynebacteria* (anaerobic):

| | |
|---|---|
| gentamicin | 1.0 gram |
| ampicillin or cephalothin | 2.0–4.0 grams |

(c) For difficult organisms very high dosages are necessary and control of infection is the overriding consideration. For a difficult *Pseudomonas* organism, the following combination might be used:

| | |
|---|---|
| gentamicin | 1.0 gram |
| amikacin | 2.0–4.0 grams |
| azlocillin | 4.0 grams |

Gentamicin remains the staple ingredient—at least 1.0 gram

# Clinical studies

- **Bi-phasic release :**
  - **peak release in the first hours, then**
  - **low release that can be measured for months.**
- **Gentamicin detected for up to 19 years, in joint fluid** (range : 0,06 to 0,85 mcg/ml) (*).
- **70% of antibiotic are locked in bone cement after many years (*)**
- **After many years, genta in tissues is only just measurable,**
- **Unless the bone cement is disrupted which causes much higher levels of antibiotic concentrations **.**

* Fletcher Acta Orthop Scand 2004; 75: 173-6

** Powles JBJS 1998. 80-B: 607-610

# ETUDES CLINIQUES

## Microbiologie sur spacer

**Two-stage revision for prosthetic joint infection: predictors of outcome and the role of reimplantation microbiology**

P. Bejon[1,2,3]*, A. Berendt[1], B. L. Atkins[1,4], N. Green[1], H. Parry[1], S. Masters[1], P. Mclardy-Smith[1], R. Gundle[1] and I. Byren[1]

Eude rétrospective, centre spécialisé (Oxford)

152 patients (PTG 77, PTH 71, coude 4)

Germes isolés à l'ablation : SCN 30%, SA 18%, strepto 7%, BGN 7%, cultures stériles 41% (PTG > PTH)

Spacer genta dans genou, rarement dans hanche (13%)

ABtt post-op IV 6 semaines IV, puis arrêt ≥ 2 semaines avant repose de prothèse

**Au 2ème temps: cultures + chez 21 patients (14%)**

Même germe (n=4), germe différent (n=10), seules cultures + au 2ème temps (n=7)

Plus fréquent dans PTG (n= 16) vs PTH (n=4); *P*=0.01

Cultures positives n'influencent pas l'évolution

**Table 2.** Factors influencing outcomes, univariate Cox regression

| Factor | HR | 95% CI | *P* value |
|---|---|---|---|
| Age of patient (per 10 years) | 0.58 | 0.4–0.9 | 0.008 |
| Age of implant (per 5 years) | 1.36 | 1.1–1.8 | 0.019 |
| Length of symptoms ≥90 days | 0.61 | 0.2–2.3 | 0.46 |
| Length of symptoms ≥1 year | 0.94 | 0.4–2.7 | 0.9 |
| Gender | 1.6 | 0.7–3.5 | 0.3 |
| Co-morbidity | 0.9 | 0.6–1.4 | 0.6 |
| Knee (versus hip) | 1.4 | 0.6–3.1 | 0.4 |
| Tertiary referral | 1.1 | 0.4–2.8 | 0.8 |
| Previous revision | 2.9 | 1.2–7.4 | 0.023 |
| Muscle flap required | 0.97 | 0.3–3.3 | 0.97 |
| Fracture occurred | 2.2 | 0.8–6.5 | 0.14 |
| Gram-negative bacilli | 0.6 | 0.1–4.7 | 0.7 |
| Streptococci | 0.4 | 0.1–3.1 | 0.4 |
| *Staphylococcus aureus* | 0.35 | 0.1–1.5 | 0.2 |
| Coagulase-negative staphylococci | 1.3 | 0.6–3.0 | 0.5 |
| Culture negative | 1.7 | 0.8–3.6 | 0.2 |
| Reimplantation microbiology | 1.3 | 0.4–3.7 | 0.6 |
| ≥4 weeks of iv antibiotics between stages | 0.78 | 0.4–1.7 | 0.5 |
| ≥1 week of antibiotics after second stage | 0.73 | 0.3–1.6 | 0.4 |

HR, hazard ratio; CI, confidence interval.

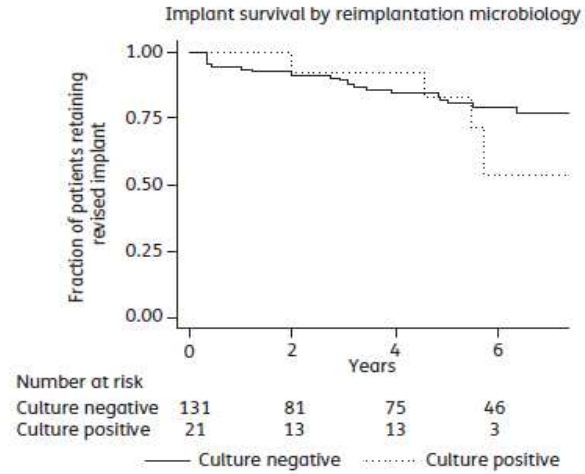


**Figure 3.** Kaplan–Meier plot showing survival of implants by reimplantation culture results.