

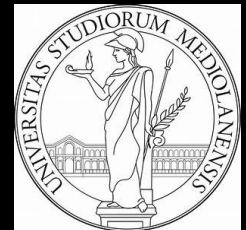
# Sicurezza ed efficacia del cemento antibiotato nella TKA

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Istituto Ortopedico Gaetano Pini, Asst Pini-CTO

UNIVERSITA' DEGLI STUDI DI MILANO

ITALY



- Introduction
- Use of Antibiotic loaded Cement (ALC) in primary TKR
- Safe use of ALC
- Efficacy of ALC
- Clinical trials
- Personal experience
- Conclusions

# Introduction

Deep infection in tkr is a devastating complication

– Garvin 1995, JBJS

• Incidence between 1,7% to 12,4%

– Robertsson 2001 Acta Ort. Scand.

– Centofanti 2005 Quad. Infezioni Articolari

Infection brings to

– An unhappy patient

– a surgeon with a tarnished reputation

– an event that is extremely costly to treat

You all agree with the importance of prevention.....



## Use of ALC in primary TKR in 2006

- Norway 1998 e Sweden -> 90% of primary TKR
- UK-> most of the surgeons
- FDA approval in 2003



Sir Neil Thomas MD, FRCS  
Past-President ESSKA

# Use of ALC in international arthroplasty registries (2023)

Acta Orthop. 2023; 94: 416–425.

PMCID: PMC10416222

Published online 2023 Aug 9. doi: [10.2340/17453674.2023.17737](https://doi.org/10.2340/17453674.2023.17737)

PMID: [37565339](https://pubmed.ncbi.nlm.nih.gov/37565339/)

The use of antibiotic-loaded bone cement and systemic antibiotic prophylactic use in 2,971,357 primary total knee arthroplasties from 2010 to 2020: an international register-based observational study among countries in Africa, Europe, North America, and Oceania

## Abstract

### Background and purpose

Antibiotic-loaded bone cement (ALBC) and systemic antibiotic prophylaxis (SAP) have been used to reduce periprosthetic joint infection (PJI) rates. We investigated the use of ALBC and SAP in primary total knee arthroplasty (TKA).

### Patients and methods

This observational study is based on 2,971,357 primary TKAs reported in 2010–2020 to national/regional joint arthroplasty registries in Australia, Denmark, Finland, Germany, Italy, the Netherlands, New Zealand, Norway, Romania, South Africa, Sweden, Switzerland, the UK, and the USA. Aggregate-level data on trends and types of bone cement, antibiotic agents, and doses and duration of SAP used was extracted from participating registries.

### Results

ALBC was used in 77% of the TKAs with variation ranging from 100% in Norway to 31% in the USA. Palacos R+G was the most common (62%) ALBC type used. The primary antibiotic used in ALBC was gentamicin (94%). Use of ALBC in combination with SAP was common practice (77%). Cefazolin was the most common (33%) SAP agent. The doses and duration of SAP used varied from one single preoperative dosage as standard practice in Bolzano, Italy (98%) to 1-day 4 doses in Norway (83% of the 40,709 TKAs reported to the Norwegian arthroplasty register).

### Conclusion

The proportion of ALBC usage in primary TKA varies internationally, with gentamicin being the most common antibiotic. ALBC in combination with SAP was common practice, with cefazolin the most common SAP agent. The type of ALBC and type, dose, and duration of SAP varied among participating countries.

Table 3. Summary of the number and types of bone cement (ALBC vs. plain) used in primary TKA recorded in each registry (2010–2020)

Register	Number of primary TKA	Type of cement	
		ALBC n (row %)	Plain n (row %)
<b>Group 1 (ALBC used in &gt; 50% of TKAs)</b>			
NJR	815,768	810,644 (99)	5,124 (0.6)
AOANJRR	414,534	393,897 (95)	20,637 (5.0)
LROI	198,764	195,155 (98)	3,609 (1.8)
EPRD	141,936	139,673 (98)	2,263 (1.6)
SAR	123,129	123,088 (100)	41 (0.04)
SIRIS	93,463	91,784 (98)	1,679 (1.8)
FAR	83,469	83,395 (100)	74 (0.1)
NZJR	73,744	60,173 (82)	13,571 (18)
DKR	49,377	37,442 (76)	11,935 (24)
NAR	40,709	40,709 (100)	0 (0)
RAR	30,816	17,818 (58)	12,998 (42)
PABZ	4,544	4,540 (100)	4 (0.1)
PANT	1,150	970 (84)	180 (16)
JointCare	839	829 (99)	10 (1.2)
<b>Group 2 (ALBC used in ≤ 50% of TKAs)</b>			
AJRR	775,697	241,866 (31)	533,831 (69)
KP	123,418	51,463 (42)	71,955 (58)
<b>Total</b>	<b>2,971,357</b>	<b>2,293,446 (77)</b>	<b>677,911 (23)</b>

**ALBC was used in 77% of the TKAs with variation ranging from 100% in Norway to 31% in the USA.**

**The primary antibiotic used in ALBC was gentamicin (94%).**

**Use of ALBC in combination with SAP was common practice (77%).**

# Safety of ALC

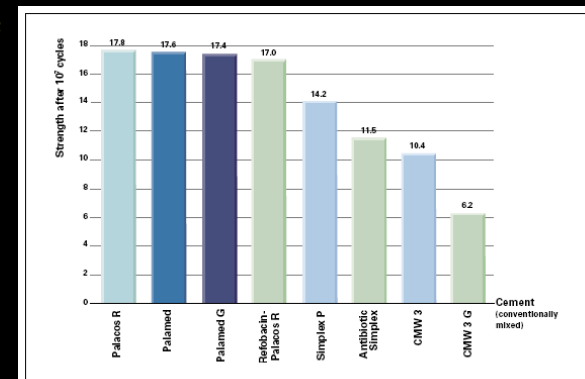
- Mechanical properties
  - High/Dose (> 2 gr. AB per 40 gr. Cement)
  - Low/Dose (< 2 gr. AB per 40 gr. Cement)

Almost zero the reduction of mechanical strength and fatigue strength if compared to standard cement

Davies 1991, J Biomed Mater Res

RSA study: no reduction in the quality of fixation

Adelberth 2002, Acta Ortop Scand



Fatigue life of Palamed and Palamed G compared to other bone cements.\*

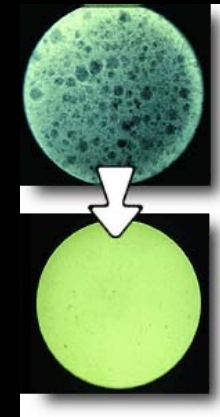
# Safety of ALC

- **ALC if correctly mixed exceeds Torque Resistance standard of 50 Mpa**
  - (Requisite rule ISO 5833)
- **Mixing system Cemvac and Optivac showed best performance af all**
- **Tested cements: Palacos R, Simplex P, CWM 1, CWM 2000, Palamed G, VersaBond**

## Comparison of various vacuum mixing systems and bone cements as regards reliability, porosity and bending strength

Hans Mau<sup>1</sup>, Katrin Schelling<sup>1</sup>, Christian Helsen<sup>1</sup>, Jian-Shang Wang<sup>2</sup> and Steffen J Breusch<sup>3</sup>

<sup>1</sup>Orthopaedic Departement, University of Heidelberg, Heidelberg, Germany, <sup>2</sup>Biomaterials and Biomechanics Laboratory, Department of Orthopedics, Lund University Hospital Lund, Sweden, <sup>3</sup>Orthopaedic Department, University of Edinburgh, Scotland  
Correspondence SB: breusch@ukonline.co.uk  
Submitted 02-06-14. Accepted 03-05-08

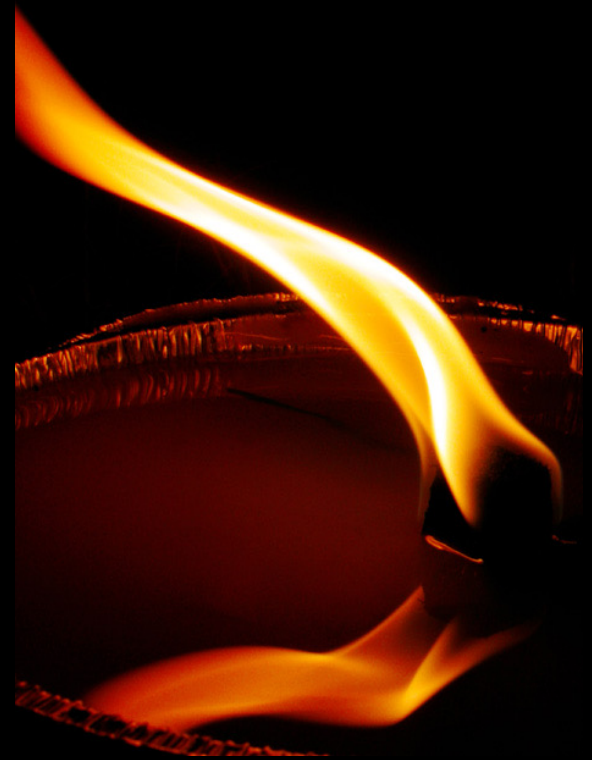


# Safety of ALC

- ALC should contain TERMOSTABLE antibiotics, that should not modify their profile of action after the polimerization.

**Table 1.** A List of Heat-Stable Antibiotics That Have Been Used in Antibiotic-Impregnated Polymethylmethacrylate Bone Cements

Gentamicin	Colistin
Clindamycin	Methacillin
Cephalothin	Tetracycline
Tobramycin	Lincomycin
Erythromycin	Dicloxacillin
Oxacillin	Bactrim
Cefuroxime	





# Safety of ALC (Allergies)










- Cefuroxime: allergic reaction only with systemic use, non in association with cement (2gr per 40gr of cement)
  - Chiu FY, Chen CM, Lin CFJ, et al: Cefuroxime impregnated cement in primary total knee arthroplasty. J Bone Joint Surg Am 84:759, 2002
- Case report in 100.000 implants with ALC: no allergic reaction
  - Bourne R., Prophylactic use of antibiotic bone cement. J of Arthroplasty 2004;4:69-72
- Gentamicin: no allergies
  - Wahlig H, Buchholz HW. Experimentelle und klinische Untersuchungen zur Freisetzung von Gentamycin aus einem Knochenzement. Chirurg (1972) 43: 441-445.
  - Penner MJ, Masri BA, Duncan CP. Elution characteristics of vancomycin and tobramycin combined in acrylic bone-cement. J Arthroplasty (1996) 11: 939-944.

## Severe Side effects with high dose ALBC-spacers?

CLINICAL RESEARCH

### Acute Kidney Injury When Treating Periprosthetic Joint Infections After Total Knee Arthroplasties with Antibiotic-Loaded Spacers Incidence, Risks, and Outcomes

 Dagneaux, Louis MD<sup>1,a</sup>;  Limberg, Afton K. BS<sup>1,b</sup>;  Osmon, Douglas R. MD<sup>1,c</sup>;  Leung, Nelson MD<sup>1,d</sup>;  Berry, Daniel J. MD<sup>1,e</sup>;  Abdel, Matthew P. MD<sup>1,f</sup> [Author Information](#) 

The Journal of Bone and Joint Surgery: March 29, 2021 - Volume Latest Articles - Issue - 10.2106/JBJS.20.01825



### Results:

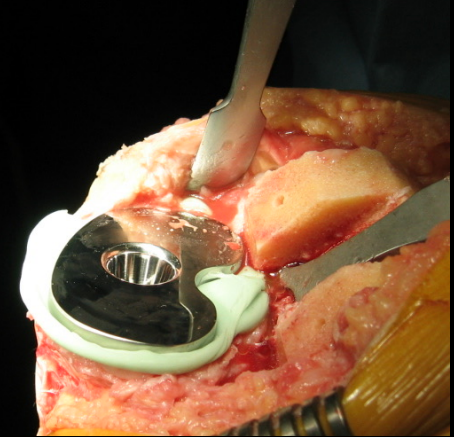
**14% patients without preexisting CKD experienced AKI vs 45% patients with prior CKD (OR 5;  $p = 0.0001$ ). Overall, when the vancomycin concentration or aminoglycoside concentration was  $>3.6$  g/batch of cement, the risk of AKI increased (OR, 1.9 and 1.8, respectively;  $p = 0.02$  for both)...**

### Conclusions:

**AKI occurred in 14% of patients with normal renal function at baseline. The risk of AKI was fivefold greater in those with preexisting CKD...**

# Safety of ALC

Most *in vitro* methods used to study gentamicin release from bone cements do not allow determination of the final concentration of gentamicin that can be obtained *in vivo*. For gentamicin-loaded Palacos R cement, however, *in vivo* measurements have been performed. On the first day after surgery, wound drainage fluids showed gentamicin concentrations of almost 50 µg/ml and 10 µg/ml for the deep and superficial drains, respectively, while on the second day these concentrations had dropped to about a quarter of these values. Concurrent serum concentrations peaked to below 1.5 µg/ml in the first hour and were undetectable after the first day, suggesting that soft tissues constitute a barrier to gentamicin diffusion.<sup>16</sup>



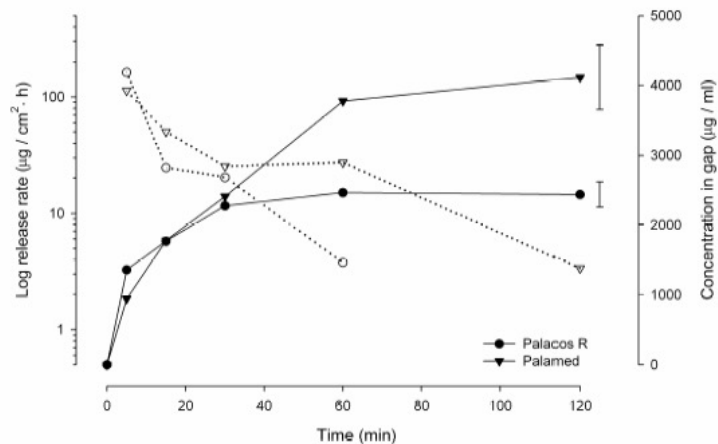
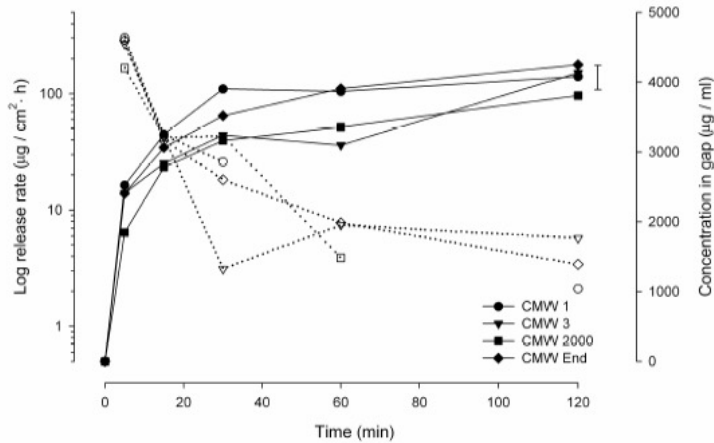
- Palacos R (gentamicin): the first day after surgery the concentration in deep drain is 50 µg/ml, superficial drain concentration is 10 µg/ml, In the second day post-op the concentration fall down to 1/4 of the initial values.
- Systemic concentration is 1.5 µg/ml (first day). The second day the concentration is not detectable (soft tissue barrier effect)
  - Wahlig H, Dingeldein E, Buchholz HW, Buchholz M, Bachmann F. Pharmacokinetic study of gentamicin-loaded cement in total hip replacements. Comparative effects of varying dosage. J Bone Joint Surg Br (1984) 66: 175-179.

# Efficacy of ALC

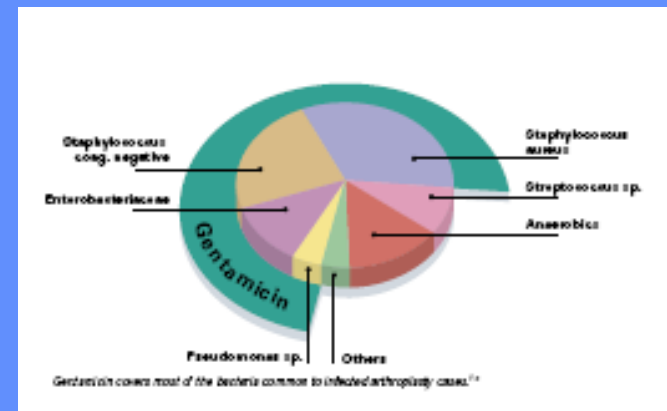
Hendriks, 2003 J Biomed Mat Res

In Gentamicin ALC the concentrations is about 1000 times higher than MIC's for staphylococci within 2 hrs from operation

More importantly, the concentrations of gentamicin found inside isolated gaps within 2 h are about 1000 times higher than MIC's for staphylococci (4 µg/ml),<sup>17</sup> being the most important species in orthopaedic implant infection.<sup>15,18,19</sup> This may be expected to effectively decontaminate the prosthesis-related interfacial gap directly after implantation, as also reflected by the fact that gentamicin-loaded Palacos R yields better short-term results than its unloaded counterpart in combination with systemic antibiotics.<sup>20</sup> Higher concentrations may



Staph. Aureo  
Pseudomonas  
Staph. Coag.-  
Enterobatt.



# Stronger and longer antimicrobial action of dual ALBC

Clin Orthop Relat Res (2008) 466:1492–1498  
DOI 10.1007/s11999-008-0203-x

ORIGINAL ARTICLE

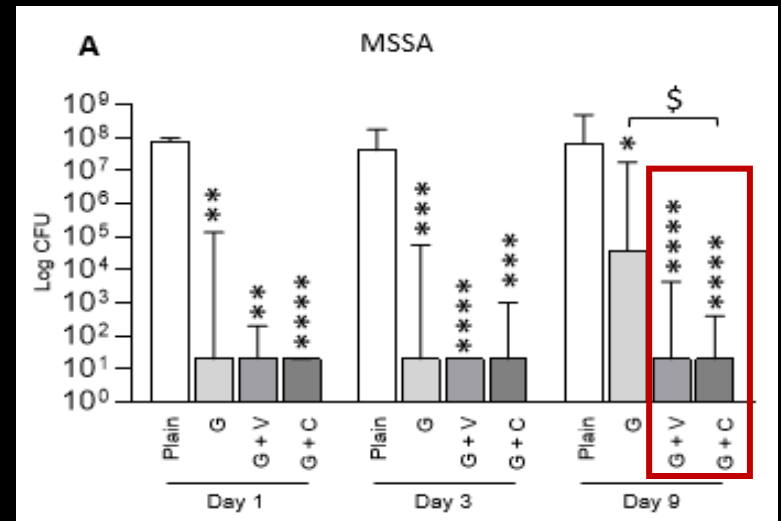
## Copal Bone Cement Is More Effective in Preventing Biofilm Formation than Palacos R-G

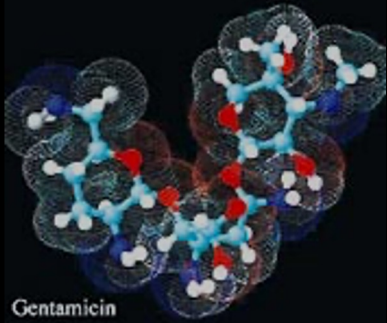
Geert T. Ensing MD, PhD, Jim R. van Horn MD, PhD,  
Henny C. van der Mei PhD, Henk J. Busscher PhD,  
Daniëlle Neut PhD

> Front Med (Lausanne). 2021 Jan 20;7:576231. doi: 10.3389/fmed.2020.576231. eCollection 2020.

## Antibiotics in Bone Cements Used for Prosthesis Fixation: An Efficient Way to Prevent *Staphylococcus aureus* and *Staphylococcus epidermidis* Prosthetic Joint Infection

Andréa Cara<sup>1</sup>, Mathilde Ballet<sup>1,2</sup>, Claire Hemery<sup>1</sup>, Tristan Ferry<sup>1,3,4,5</sup>, Frédéric Laurent<sup>1,2,3,5</sup>, Jérôme Josse<sup>1,3,5</sup>





# Drug resistance for ALC (Gentamicin)

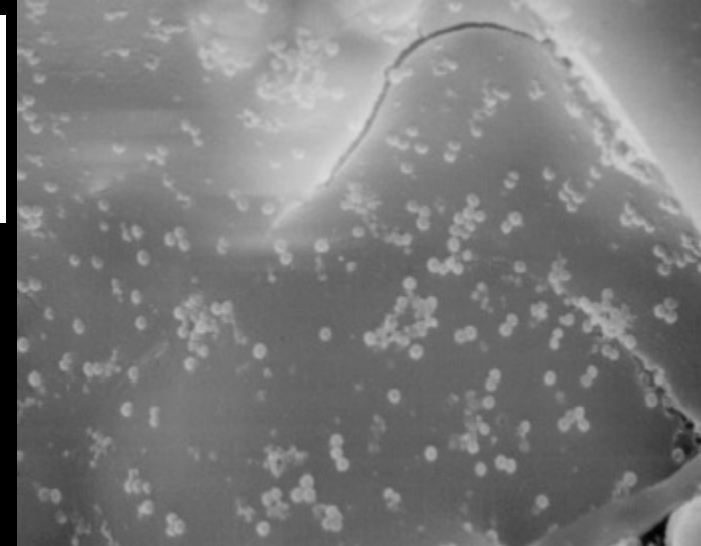


Bacterial survival in the interfacial gap in gentamicin-loaded acrylic bone cements

VOL. 87-B, No. 2, FEBRUARY 2005

J. G. E. Hendriks,  
D. Neut,  
J. R. van Horn,  
H. C. van der Mei,  
H. J. Busscher

analyses.<sup>30,31</sup> Our study confirms the efficacy of gentamicin-loaded cement. However, it also points out that gentamicin-loaded cement may select for gentamicin-resistant strains. Similar observations have been made in clinical practice.<sup>9,32</sup>

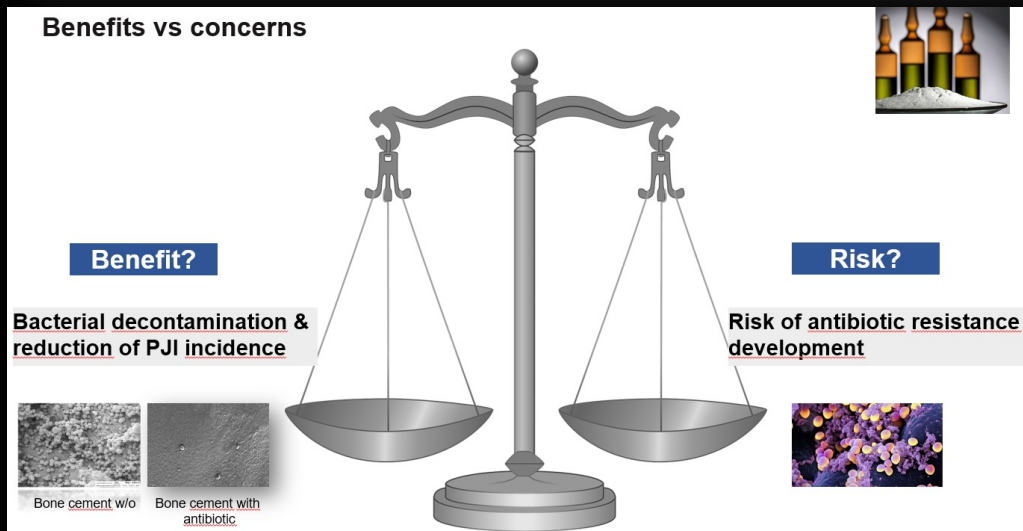


Gentamicin resistant strains can develop years from the operation, with hematogenous dissemination and only by Staphylococci Coagulase Negative (strain CN5115)

Ev. Revision with ALC with Vancocin

## Risk assessment of antibiotic resistance development by antibiotic-loaded bone cements: is it a clinical concern?

[Christof Berberich](#)<sup>1</sup> and [Pablo Sanz-Ruiz](#)<sup>2</sup>



...The benefit of a lower infection probability with combined systemic and local antibiotic application should outweigh the risk of more resistant bacteria. There is no clinical evidence that the routine use of bone cement impregnated with appropriate bactericidal antibiotics promotes the widespread development of antibiotic resistance among the pathogens causing PJI...

# Drug resistance for ALC

- ALC (Gentamicin + 1 gr. of Vancocin) can prevent MRSA

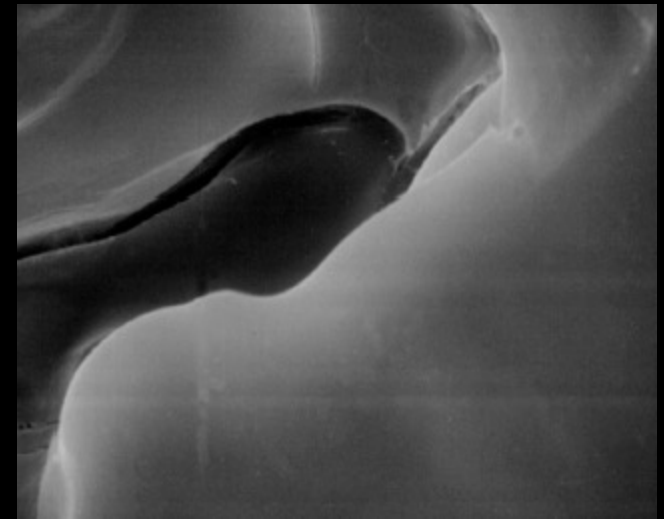
*Biomed. Papers 149(1), 153-158 (2005)*

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© J. Gallo, M. Kolář, A. V. Florschütz, R. Novotný, R. Pantůček, M. Kesselová

## **IN VITRO TESTING OF GENTAMICIN-VANCOMYCIN LOADED BONE CEMENT TO PREVENT PROSTHETIC JOINT INFECTION**

Jiří Gallo<sup>a\*</sup>, Milan Kolář<sup>b</sup>, Anthony V. Florschütz<sup>c</sup>, Radek Novotný<sup>d</sup>, Roman Pantůček<sup>e</sup>,  
Michaela Kesselová<sup>b</sup>



Gentamicin-vancomycin loaded PMMA completely inhibited any bacterial growth.



# Price of ALC

- Refobacin Plus costs 30% more than Cement without AB



Knee Surgery, Sports Traumatology, Arthroscopy (2023) 31:3847–3853  
<https://doi.org/10.1007/s00167-023-07364-5>

KNEE



## Routine use of antibiotic-laden bone cement in total knee arthroplasty is a cost-effective practice in the single-payer healthcare system

Hassaan Abdel Khalik<sup>1</sup> · Thomas J. Wood<sup>1,2</sup> · Daniel M. Tushinski<sup>1,2</sup> · Aaron Gazendam<sup>1</sup> · Danielle T. Petruccelli<sup>1,2</sup> · Kamal Bali<sup>1,2</sup> · Hamilton Arthroplasty Group · Mitchell Winemaker · Victoria Avram · Justin de Beer · Dale Williams · Laura Puri · Liz Piccirillo

Received: 3 December 2022 / Accepted: 21 February 2023 / Published online: 11 March 2023  
© The Author(s) under exclusive licence to European Society of Sports Traumatology, Knee Surgery, Arthroscopy (ESSKA) 2023

# Clinical Trials

(prospective)

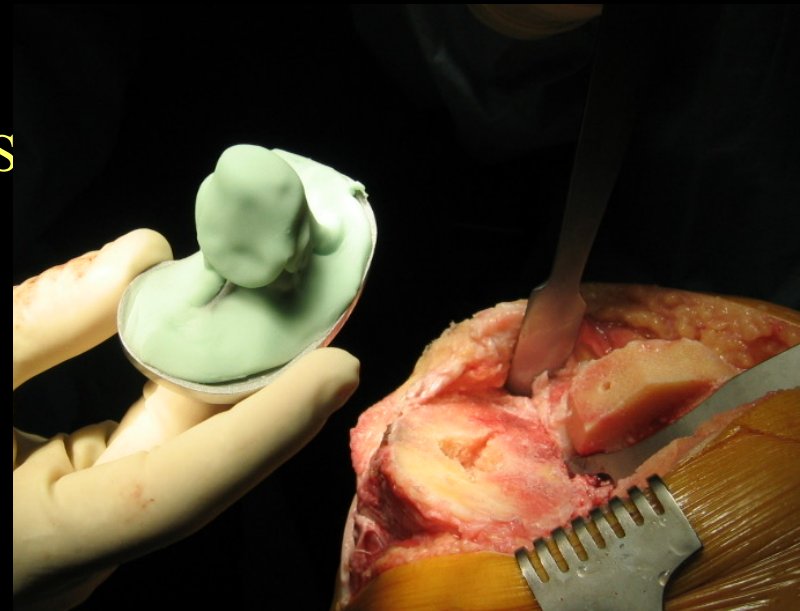
- Chiu (2002 JBJS), prospective, 340 cemented TKR (+/- Cefuroxime) with an important reduction in infections (0 vs 3)
- Chiu (2001 JBJS), 78 pt DIABETICS with cemented TKR (Cefuroxime) 0% infections

## CEFUROXIME-IMPREGNATED CEMENT IN PRIMARY TOTAL KNEE ARTHROPLASTY

A PROSPECTIVE, RANDOMIZED STUDY OF THREE HUNDRED AND FORTY KNEES

BY FANG-YAO CHIU, MD, CHUAN-MU CHEN, MD, CHIEN-FU JEFF LIN, MD, PHD, AND WAI-HEE LO, MD

THE JOURNAL OF BONE & JOINT SURGERY · JBJS.ORG  
VOLUME 84-A · NUMBER 5 · MAY 2002



# Clinical Trials

(systematic review)

Systematic Review and Meta-Analysis

Medicine®

OPEN

## Antibiotic-impregnated bone cement for preventing infection in patients receiving primary total hip and knee arthroplasty

### A meta-analysis

Jin Zhang, MA<sup>a,b</sup>, Xiao-Yu Zhang, MA<sup>a</sup>, Feng-Li Jiang, MA<sup>a</sup>, Yi-Ping Wu, BS<sup>a</sup>, Bei-Bei Yang, MA<sup>a</sup>, Zi-Yun Liu, BS<sup>a</sup>, Dong Liu, MA<sup>a,c,\*</sup>

2019

**Conclusions:** AIBC may significantly decrease deep infection rates after primary total hip and knee arthroplasty, with or without systemic antibiotics.


## Recent Analysis of the UK Registries (NJR-2019)



The Bone & Joint Journal, Vol. 101-B, No. 11 | Knee

### Antibiotic-loaded bone cement is associated with a lower risk of revision following primary cemented total knee arthroplasty

An analysis of 731 214 cases using National Joint Registry data

Simon S. Jameson , Asaad Asaad, Marina Diament, Adetatyo Kasim, Theophile Bigirumurame, Paul Baker, James Mason, Paul Partington, Mike Reed

Published Online: 1 Nov 2019 | <https://doi.org/10.1302/0301-620X.101B11.BII-2019-0196.R1>

ALBC was associated with a lower risk of revision for all aseptic causes (**HR 0.85**,  $p < 0.001$ ) and revisions for infection (HR 0.84,  $p = 0.06$ ).

The Bone & Joint Journal, Vol. 102-B, No. 8 | Hip

### Is the use of antibiotic-loaded bone cement associated with a lower risk of revision after primary total hip arthroplasty?

A study of 418,857 total hip arthroplasties in the National Joint Registry for England, Wales, Northern Ireland and the Isle of Man

Justin W. Leonard , Michael I. Cook, Terence W. O'Neill, Timothy N. Board

The risk of revision for infection was lower with ALBC (**OR 0.77**)...even for aseptic loosening of stem (OR 0.53) or socket (OR 0.46)



# Clinical Trials

(retrospective)

- Bourne R (J of Arthroplasty 2004)



## 1st group

493 TKR

Op. Room Standard

Simplex + Eritromicin and Colistin

0.6% deep infections

## 2nd group

668 TKR

Laminar flow

Simplex (no ALC)

0.6% deep infections

- Conclusions: ALC is as effective as laminar flow

# Our case serie

## Policlinico San Donato



# First Serie

## Standard Op. environment

- Feb. 2001- Feb 2003:
  - 55 Knee arthroplasties (55 pts, 5 uni, 9 revisions)

## 2 INFECTIONS

- Cement: Simplex
- CKS Stratek, Oxford 3 Biomet

# Second Serie

- March 2003-july 2006:
  - 176 Knee Arthroplasties (164 pts, 12 bilat, 30 uni, 8 revisions)

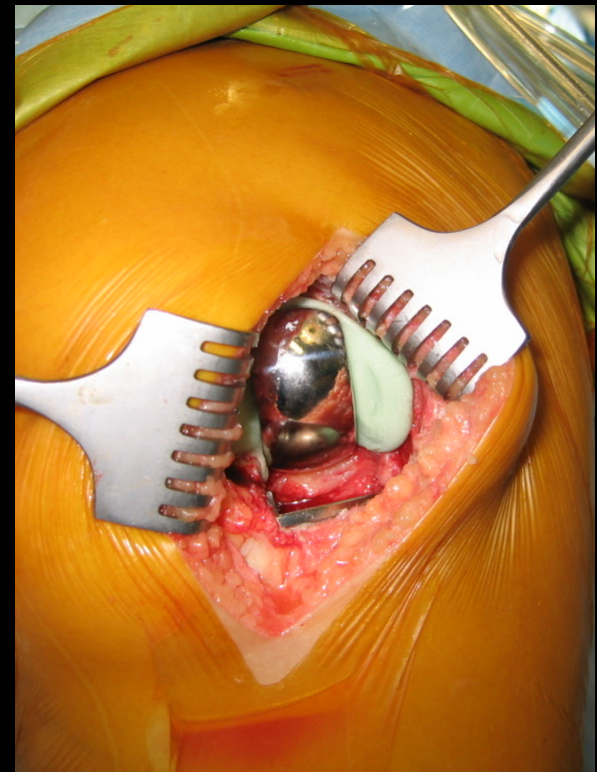
## ZERO INFECTIONS

- Cement: PALAMED G
- CKS Stratek, PFC Sigma J&J, Oxford 3 Biomet



# STATISTICS

- $P = 0,056$  weak dependence but still correlation between the absence of infections and the use of ALC (Fisher's exact test)



# Conclusions

- Literature and our experience show that ALC is effective in deep infections reduction without affecting the outcome of the implants
- There is no report about complications related to the use of ALC
- We suggest the use of ALC in case of:
  - No laminar flow
  - Pt that used antibiotics in the year prior to surgery
  - Immunodeficiency
  - Diabetics
  - Older than 75 y.o.
  - Revisions
- Even when using ALC, surgeons MUST carefully respect the antiseptis rules





*Thank you*

[pietro.randelli@unimi.it](mailto:pietro.randelli@unimi.it)