Session Infection

# Update on the use of local antimicrobials in musculoskeletal infection

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*Manager bonebank*
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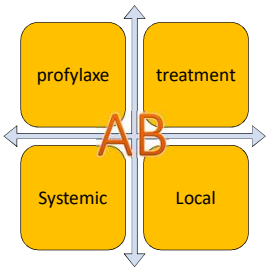
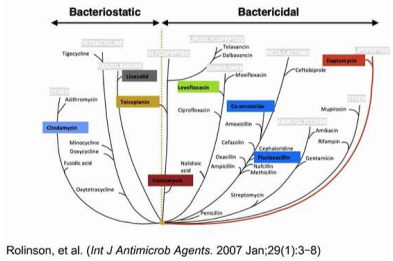
Complications in Orthopaedics and Traumatology
25-26 April 2019
Kursaal Oostende

## Overview

- biofilm
- Toxicity
- Carrier
- Literature




## Unfamiliar territory for an orthopaedic surgeon …




Rolinson, et al. (*Int J Antimicrob Agents*. 2007 Jan;29(1):3–8)

## Solution: Orthopaedic Infection Round


**Pocket Guide to Diagnosis & Treatment of Periprosthetic Joint Infection (PJI)**

PRO-IMPLANT FOUNDATION

Version 8:
1 March 2018

Contact our Consultation Portal for recommendations: cs.pro-implant-foundation.org
Register for PRO-IMPLANT Workshops: www.pro-implant-foundation.org

- **CLASSIFICATION**
- **DIAGNOSTIC ALGORITHM**
- **SURGICAL PROCEDURES**
- **TREATMENT ALGORITHM**
- **RECOMMENDED ANTIMICROBIAL TREATMENT**

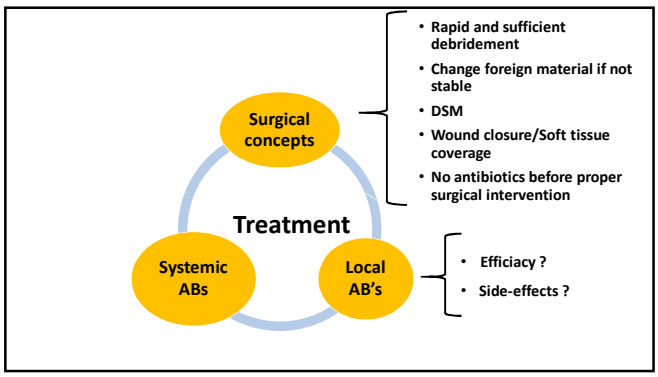
- **LOCAL ANTIMICROBIALS IN BONE CEMENT (PMMA)**
  **(additionally to systemic antimicrobial treatment)**

## Solution: Orthopaedic Infection Round

→ Longlasting systemic AB treatment and debilitating two-stage surgical treatments

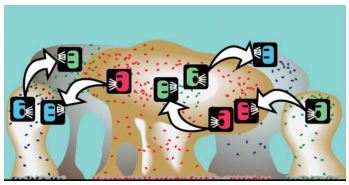
→ **treatment failures**

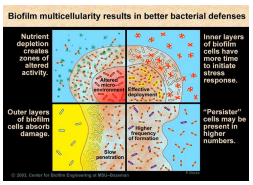
**Final responsibility for the surgeon !!**



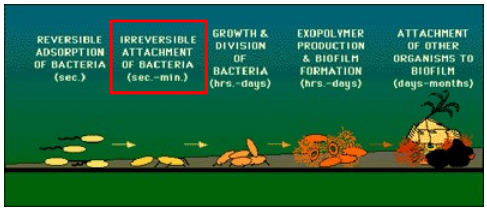

## Biofilm on bone and implants

Costerton JW. **Biofilm theory** can guide the treatment of device-related orthopaedic infections. Clin Orthop Relat Res **2005**(437):7-11.






## Run for the surface




**Biofilm is mature after 3 weeks!**

## Definitions

- MIC : minimum inhibitory concentration preventing visible growth of bacterium
- MBC : minimum bactericidal concentration = result in a 3-log reduction (planktonic)
- MBEC : Minimum biofilm eradication concentration to kill all the bacteria in a biofilm can be **hundreds to thousands-times higher** than the MIC

TREATMENT

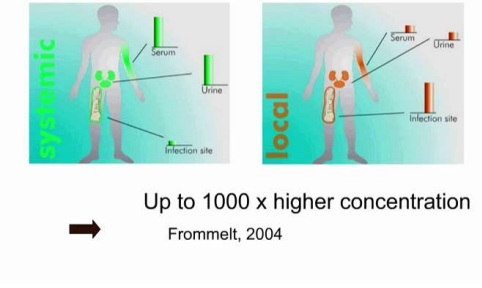
## Sensitivity sessile – planktonic MBEC vs MIC

| Bacterium | | Penicillin G | Cloxacillin | Streptomycin | Ceftiofur | Tetracycline |
|---|---|---|---|---|---|---|
| *Arcanobacterium* | MIC | < 2 | < 2 | 4 | < 2 | < 2 |
| *pyogenes* | MBEC | > 1024 | > 1024 | 256 | > 1024 | > 1024 |
| *Staphylococcus* | MIC | 2 | < 2 | 128 | < 2 | < 2 |
| *aureus* | MBEC | > 1024 | 512 | > 1024 | 256 | 512 |
| *Staphylococcus* | MIC | 16 | < 2 | 512 | < 2 | 32 |
| *hyicus* | MBEC | > 1024 | 4 | > 1024 | 128 | 256 |
| *Streptococcus* | MIC | < 2 | < 2 | 64 | < 2 | < 2 |
| *agalactiae* | MBEC | > 1024 | > 1024 | 256 | > 1024 | > 1024 |
| *Streptococcus* | MIC | < 2 | < 2 | 32 | < 2 | < 2 |
| *dysgalactiae* | MBEC | < 2 | < 2 | 64 | < 2 | 4 |
| *Streptococcus suis* | MIC | < 2 | < 2 | 128 | < 2 | 32 |
| | MBEC | 8 | < 2 | 128 | < 2 | 32 |
| *Corynebacterium* | MIC | < 2 | < 2 | 16 | < 2 | < 2 |
| *renale* | MBEC | > 1024 | > 1024 | 128 | > 1024 | 1024 |
| *Corynebacterium* | MIC | < 2 | < 2 | 256 | < 2 | < 2 |
| *pseudotuberculosis* | MBEC | > 1024 | > 1024 | 256 | 1024 | 256 |

MIC — minimum inhibitory concentration; MBEC — minimum biofilm eradication concentration

*Olson ME, Ceri H, Morck DW, Buret AG, Read RR. Biofilm bacteria: formation and comparative susceptibility to antibiotics. Can J Vet Res 2002;66:86-92.*

## Antibiotics




Up to 1000 x higher concentration

Frommelt, 2004

# TOXICITY

**Local:** Summary of studies performing **cell line experiments**

| | | | |
|---|---|---|---|
| Antoci V, | 2007 | **Cipro / Tobra / Vanco** | preosteoblasts, prechondrocy-tes |
| Edin ML, | 1996 | **Cefazolin / Vancomycin** | MG-63 osteoblast |
| Ince A, | 2007 | **Gentamicin** | C2C12 cells |
| Kucera T, | 2017 | **Gentamicin / Vancomycin** | Mesenchyma l Stem Cells |
| Lewis CS | 2011 | **Gentamicin** | Rat calvarial osteoblasts |
| Miclau T | 1995 | **aminoglycosides.** | MG-63 osteoblast |
| Naal FD, | 2008 | **clindamycin** | Human osteoblasts |
| Pilge H | 2016 | **Cefazolin** | Bone marrow mononuclear cells |
| Rathbone CR | 2011 | **21 antibiotics** | Human osteoblasts |
| Salzmann GM | 2007 | **cefuroxime** | Human osteoblasts |

## Conclusions:

**Vancomycin** was found to be the least osteotoxic antibiotic. It has a favorable elution profile both *in vitro* and *in vivo* due to its ideal molecular weight. ***(gram +)***

**Tobramycin** appears to be less osteotoxic compared to **gentamicin** ***(gram -)***

**Systemic :** summary of animal studies and human trials

**The serum levels of locally used antibiotics are typically too low to cause systemic effects**.

*Turner TM, Local and systemic levels of tobramycin delivered from calcium sulfate bone graft substitute pellets. Clin Orthop Relat Res 2005*

*Wahlig H, The release of gentamicin from polymethylmethacrylate beads. An experimental and pharmacokinetic study J Bone Joint Surg Br 1978*

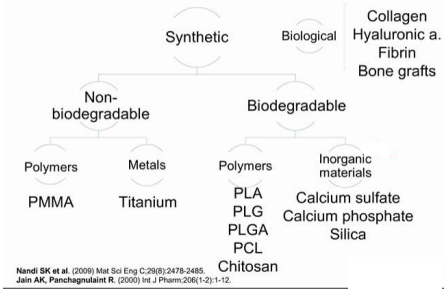
*Eckman JB, Wound and serum levels of tobramycin with the prophylactic use of tobramycin-impregnated polymethylmethacrylate beads in compound fractures. Clin Orthop Relat Res 1988*

*Walenkamp GH, Gentamicin-PMMA beads. Pharmacokinetic and nephrotoxicological study. Clin Orthop Relat Res 1986*

**To date, no known cases of allergic reaction to local antibiotics have been published.**

# CARRIER

## Biomaterials as carrier:

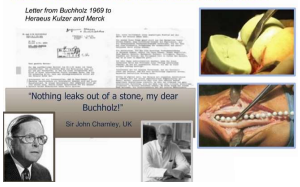



Nandi SK et al. (2009) Mat Sci Eng C;29(8):2478-2485.
Jain AK, Panchagnulaint R. (2000) Int J Pharm;206(1-2):1-12.

## PMMA

**Buchholz and Engelbrecht 1970**

**Idea of using polymethylmethacrylate (PMMA) as local antibiotic carrier dates back to the 1960s**




Prohylaxis (prosthetic fixation)

**Klemme 1979**

**Polymethylmethacrylate (PMMA) beads**

Difficult to get "off the shelf"

- Pros
  - Good local AB delivery
  - Well known procedure
  - Removal without second operation < 10 days
- Cons
  - Application not always easy
  - Removal after > 10 days can be difficult
  - Risk of rupture
  - No stability at all

Treatment (spacer, beads)

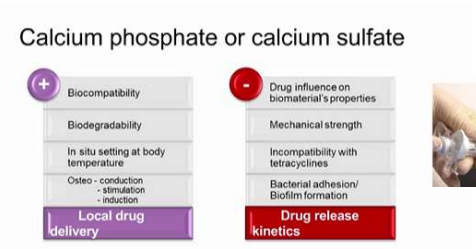
## Nonbiodegradable bone cements- PMMA


**a rapid release during the initial 24 h, steep decline , steady decline : surface phenomenon**

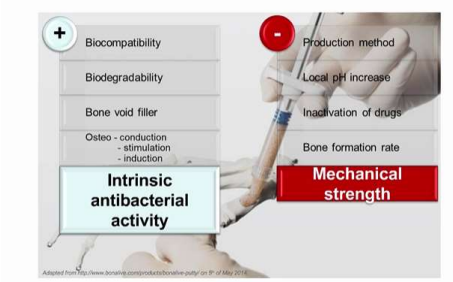
***Anagnostakos . Elution of gentamicin and vancomycin from PMMA beads and hip spacers in vivo. Acta Orthop 2009***

## Biodegradable bone cements

Calcium phosphate or calcium sulfate




## Bioactive glass




## Collagen fleece with AB (sponges)

- Pros
  - Good local AB delivery
  - Quick application
  - Hemostasis
- Cons
  - Application difficult in diaphysis
  - Short time of delivery **(< 72 h)**
  - "Homemade" impossible
  - Residuum
  - No stability

Gentamicinsulfate, ie, Gentafleece

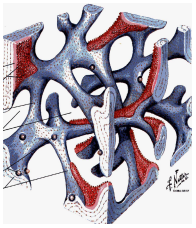
## Biologicals : bone graft

Cancellous Bone

- Large surface
- Storage capabilty
- Solid structure
- Slow resorption

↓

IDEAL CARRIER ?



## Review:

KU LEUVEN FACULTY OF MEDICINE

**Current insights in the application of bone grafts for local antibiotic delivery in bone reconstruction surgery.**

Master Thesis proposed to achieve the degree of master in medicine by

**Arne PEETERS**
KU Leuven
Faculty of medicine

Promotor: **Prof. dr. Lieven THORREZ**
Mentor: **dr. Guy PUTZEYS**
Leuven, **2018-2019**

PRISMA flowchart
524 → 48 articles

## Conclusion

**Despite great variance in methodology** it was possible to conclude that bone grafts are **suitable for local antibiotic application**.

**Several approaches** result in **high initial antibiotic concentrations, essential for biofilm eradication**.

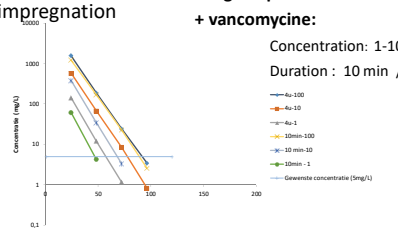
**not inducing osteoblast toxicity and not affecting bone incorporation.**

Therapeutically, a **single stage procedure** in the treatment of bone infection seems feasible.

## AZ groeninge in vitro solution impregnation study:

**0.5 g deepfrozen cleaned bone chips + vancomycine:**

Concentration: 1-10-100 mg/ml
Duration : 10 min / 4 hours



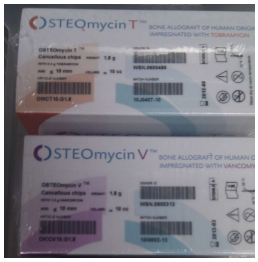

- impreg-conc 100 mg/ml **after 96 h no therapeutic concentration**
  At lower concentrations even earlier

- impregnation-conc looks more important than impregnation-duration

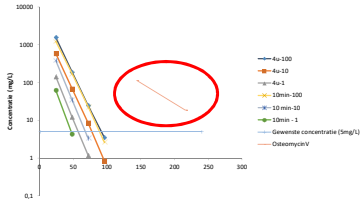
## Antibiotic impregnated bone matrix: OsteomycinV® or T®

Dr Heinz Winkler

- 400mg Tobramycin / 10cc (Gram -)
- 1000mg Vancomycin / 10cc (Gram +)




## Comparison with OsteomycinV measurement after 6 days and 8 days (immuno-assay)




**-Osteomycin V significant longer elution time above the desired conc**

-Similar with results of Winkler 2000, similar chromatography

## One stage procedures

- Follow up >2y Heinz Winkler 2015
  - 88 Hips / 6 Re-Infections
  - 68 Knees / 5 Re-Infections
  - 52 Osteosyntheses / 3 Re-Infections

Total:
**208** One Stage Revisions / **14** Re-Infections

93% Infection free – with 1 OP!

## Conclusion

- Local AB are an essential part of the treatment of PJI and FRI
- Vancomycine (gr +) and tobramycine (Gr-) are safe to use locally
- Current carriers have suboptimal release characteristic for treatment

  Bonegraft seems promising
- One stage surgery
- Weak clinical scientific evidence