AN OVERVIEW
OF DIFFERENT APPLICATIONS
OF LOCAL ANTIBIOTIC THERAPY
IN THE PREVENTION OF PJI

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Athens Medical School - University Hospital ATTIKON
DISCLOSURES

Nothing to disclose for this presentation
INFECTION PREVENTION MEASURES

• Risk factor correction (Diabetes, Ca, immunosuppresion, poor nutrition, hypoabuminemia, other infections eg SSTIs, UTIs)
• Careful pre-operative evaluation for occult infection
• Short preoperative period
• Proper pre- and intra-operative measures
• Shorter duration of operation
• Clean air in the operating field (eg. laminar flow)
• Surgical site infection surveillance (SSIs)
• Decolonization of MRSA
• Antibiotic chemoprophylaxis
• Antibiotic impregnated cement

Walenkamp G, EFORTE 2001
Matar WY, JBJS Am 2010
Widmar A, ESCMID Post. Course 2015
Mohajer MA & Darouiche RO, J Appl Biomater Funct Mater 2014
Kapadia BH, Lancet 2015
Kluymans J, ECCMID 2003
Berbari EF, CID 1998
Palumbo VD, Life Safety Secur 2017
Goals and Principles of Antibiotic Prophylaxis

• It is not an attempt to sterilize tissues, but rather to reduce the microbial flora of intraoperative contamination to a level that it can be effectively managed by the host defenses.

• The goal is to achieve serum and tissue drug levels > MIC for the most likely pathogen and for the duration of the operation.

• Agent with the narrowest spectrum of activity

Bratzler DW, CID 2004 & ASHP Report, Am J Health Syst Pharm 2013
Meehan J, JBJS Am 2009
There is no evidence that antibiotics will hinder infections caused by poor surgery.
MOST LIKELY PATHOGENS IN PJIs

• Coagulase negative Staphylococci (CNS) 20-43%
• Staphylococcus aureus 12-25%
• Polymicrobial 10-20%
• Gram-negative bacteria 3-20 %
• Streptococcus spp 8-10%
• Anaerobes eg. P.acnes (shoulder TJA up to 17%) 2-10%
• Enterococcus spp 3-7%
• Candida sp, Brucella sp, Mycobacterium sp, C.acnes rare*
• Pathogen not detected 8-19%

• * rate may be increased due to anti-TNF usage for RA

Widmer A.F, Clin Infect Dis 2001; 33:94-1
KINETICS OF S.epidermidis BIOFILM FORMATION

Time frame to prevent bacterial adhesion and biofilm formation

Hola V et al, Scr Med 2006
LOCAL ANTIBIOTIC TREATMENT AS PROPHYLAXIS IN PJA

RATIONALE

- Form an effective colonization barrier around the implant
- Prevention of rapid biofilm formation
- High concentration of locally released antibiotics (x100-x1000 MIC)
- May overcome moderately resistant strains locally
- Low systemic antibiotic concentration
- Various antibiotics available against Gram (+) & (-) bacteria
CARRIERS OF ANTIBIOTICS (examples)

- Polymethylmethacrylate (PMMA)
  - bone cement, spacers, chains, rods
- Collagen sponges
- Ceramic biocomposites (e.g. calcium sulphate – plaster of Paris,
  calcium phosphate, hydroxyapatite)
- Bone substitutes
- Coated implants

Biodegradable (e.g. bone substitute, ceramic)
Non-biodegradable (e.g. PMMA cement, spacers, beads)

Antibiotic delivery
- commercially premixed ready-to-use products (e.g. aminoglycosides,
  vancomycin)
- hand-made by surgeons products

FOR PROPHYLAXIS
- Bone cement
- Sponges

Ferguson J, Diefenbeck M, McNally M. J Bone Joint Infect 2017
Berbari E, Baddour LM. Up To Date 2019
Cemented hip endoprosthesis

1. Bone cement
2. Prosthesis stem
3. Artificial acetabular cup
HAND MIXING OF ANTIBIOTIC TO BONE CEMENT

ANTIBIOTICS IN BONE CEMENT
Bacteriologic, physical and chemical factors required

• Thermally stable (high polymerization temperature) and water soluble
• Broad antimicrobial coverage
• Available as a powder
• Low incidence of allergy, toxicity and resistance
• Must not significantly compromise mechanical integrity
  \( \leq 10\% \text{ or} \leq 4\text{ g per 40 g PMMA} \)
• Appropriate elution from the cement
• Good bone and cell penetration
• High initial release and high local concentration

Ranjan RK et al, Inter J Orthop Sci 2017
### EXAMPLES OF INDUSTRIAL MANUFACTURED ALBC

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>product</th>
<th>Antibiotic (for primary TJA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heraeus</td>
<td>Palacos R+G</td>
<td>Gentamycin 0.5 / 1 g</td>
</tr>
<tr>
<td>DePuy</td>
<td>Smartset GHV</td>
<td>Gentamycin 0.5/1 g</td>
</tr>
<tr>
<td>Stryker</td>
<td>Pimplex P</td>
<td>Tobramycin 1 g</td>
</tr>
<tr>
<td>Biomet</td>
<td>Refobacin R</td>
<td>Gentamycin 0.5 g</td>
</tr>
</tbody>
</table>

Fillingham Y et al, J Arthroplasty 2019

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Product</th>
<th>Antibiotics</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomet</td>
<td>Refobacin revision</td>
<td>1.0 g gentamycin 1.0 g clindamycin</td>
<td>One- or two-stage revision for PJI caused by gentamycin and clindamycin-sensitive bacteria</td>
</tr>
<tr>
<td>Heraeus</td>
<td>Copal G+C</td>
<td>1.0 g gentamycin 1.0 g clindamycin</td>
<td>Revision for PJI caused by gentamycin- and clindamycin-sensitive bacteria</td>
</tr>
<tr>
<td></td>
<td>Copal G + V</td>
<td>0.5 g gentamycin 2.0 g vancomycin</td>
<td>Single- or two-stage revision of proven severe PJI by pathogens sensitive to vancomycin (such as MRSA/ MRSE)</td>
</tr>
<tr>
<td>Stryker</td>
<td>Simplex P with Tobramycin</td>
<td>1.0 g tobramycin</td>
<td>“For the fixation of prostheses to living bone in the second stage of a two-stage revision for total joint arthroplasty”</td>
</tr>
</tbody>
</table>

ANTIBIOTIC RELEASE FROM PMMA BEADS

Anagnostakos K et al, Acta Orth 2009
In Vitro Antibiotic Release Characteristics of Antibiotic-Loaded Bone Cement

**In vitro Vancomycin [μg/mL] / Day**

- 4 g of vancomycin powder per 40-g PMMA

**In vitro Vancomycin [μg/mL] / Day**

- 2 weeks!!
- 16 μg/ml

4 g of vancomycin powder per 40-g PMMA

Hsu et al. JBJS (am) 2017
In vitro elution of moxifloxacin and fusidic acid by a synthetic crystalline semihydrate form of calcium sulphate (Stimulan™)

Periklis Panagopoulos, Thomas Tsaganos, Diamantis Plachouras, Dionyssia-Pinelopi Carrer, Antonios Papadopoulos, Helen Giamarellou, Kyriaki Kanellakopoulou*

4th Department of Internal Medicine, University of Athens, Medical School, Athens, Greece

Fig. 1. Elution of moxifloxacin by Stimulan™. S.D., standard deviation.

Fig. 2. Elution of fusidic acid by Stimulan™. S.D., standard deviation.
ANTIMICROBIAL ACTIVITY OF VARIOUS ANTIBIOTICS AGAINST INTRAOSTEOBLASTIC S. AUREUS

ACTION INTRACELLULAIRE À CONCENTRATION OSSEUSE

![Graph showing the antimicrobial activity of various antibiotics against intraosteoablatic S. aureus.](source: Valour et al., BJI Study Group, Antimicr Agents Chemother, 2015)
ANTIBIOTIC COMBINATIONS IN BONE CEMENT

• Broader spectrum of activity
• Reduced risk of resistance
• Synergistic release effect: Gentamycin + vancomycin 
  + ciprofloxacin/levofloxsasin
  + daptomycin
  + clindamycin
  + colistin

Time kill curves of S.aureus showing synergism between vancomycin and aminiglycosides

Watanakunakom C & Tisone J, AAC 1982
Rochon-Edouard S, AAC 2000
Kuhn KP, PMMA Cements, Springer 2014
Kuhn KD et al, Maitrise Orthop 2015
## ANTIBIOTICS THAT CANNOT BE USED WITH BONE CEMENT

<table>
<thead>
<tr>
<th>Situation</th>
<th>Antibiotic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interference with PMMA polymerization</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Disturbance of mechanical strength</td>
<td>Liquid antibiotics</td>
</tr>
<tr>
<td>Thermal stability</td>
<td>Flucloxacillin, imipenem, tetracycline</td>
</tr>
<tr>
<td>Allergy</td>
<td>Penicillins</td>
</tr>
</tbody>
</table>

Kendof D, Periprosthetic joint infections, Springer, 2016
EVIDENCE FROM REGISTRIES, RANDOMIZED TRIALS AND META-ANALYSES
Prevention of deep infection in joint replacement surgery

DATA FROM NATIONAL REGISTRIES

Prosthesis survival with revision due to infection as endpoint following 45,250 primary total hip replacements, performed in Norway in 1987–2007, where no antibiotic prophylaxis (None), intravenous antibiotic prophylaxis (S), antibiotic-impregnated cement (C), or both intravenous antibiotic prophylaxis and antibiotic-impregnated cement (SC) was used.

Jamsen E, Acta Orthop 2010
## Prevention of deep infection in joint replacement surgery

### DATA FROM NATIONAL REGISTRIES (TKA)

<table>
<thead>
<tr>
<th>REGISTRY</th>
<th>No of Primary TKA</th>
<th>ALBC Antibiotic –loaded Bone Cement Revision rate</th>
<th>Plain Cement Revision rate</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finnish</td>
<td>43.149</td>
<td></td>
<td></td>
<td><strong>1.35 (1.01-1.81)</strong></td>
</tr>
<tr>
<td>Australian</td>
<td>&gt; 100.000</td>
<td>5.4 % (any cause) 0.4 % (infection)</td>
<td>5.3% (any cause) 0.5 % (infection)</td>
<td>1.07 No difference</td>
</tr>
<tr>
<td>Canadian</td>
<td>&gt; 20.000</td>
<td>1.4 %</td>
<td>1.51 %</td>
<td>No difference</td>
</tr>
<tr>
<td>USA</td>
<td>22.889</td>
<td><strong>1.4 % (infection rate)</strong></td>
<td>0.7 % (infection rate)</td>
<td>P=0.002 OR 1.7, p=0.012</td>
</tr>
</tbody>
</table>

Australian Orthopaedic Association 2014, [https://aoanjrr.dmac.adelaide.edu.au](https://aoanjrr.dmac.adelaide.edu.au)  
Bohm E et al, Clin Ortop Relat Res 1990  
Namba RS et al, J Arthroplasty 2009
## Prevention of deep infection in joint replacement surgery

### DATA FROM RANDOMIZED STUDIES AND COMPARATIVE SERIES (TKA)

<table>
<thead>
<tr>
<th>STUDY</th>
<th>No of TJA</th>
<th>ALBC (Antibiotic – loaded Bone Cement Infection rate)</th>
<th>Plain Cement Revision rate</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chiu et al, Taiwan</td>
<td>340 - TKA</td>
<td>0 cefuroxime</td>
<td>3.1 %</td>
<td>p=0.023</td>
</tr>
<tr>
<td>prospective, random</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gandhi et al, Canada</td>
<td>1625 TKA</td>
<td>2.2 % tobramycin</td>
<td>3.1 %</td>
<td>p=NS</td>
</tr>
<tr>
<td>prosp. non-randomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hinarejos et al, Spain</td>
<td>2948 – TKA</td>
<td>1.35 % erythromycin colistin</td>
<td>1.4 %</td>
<td>p=NS</td>
</tr>
<tr>
<td>prospective randomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Namba et al, USA,</td>
<td>22.889 - TKA</td>
<td>1.4 % tobtamycin gentamycin</td>
<td>0.7 %</td>
<td>p=0.002</td>
</tr>
<tr>
<td>retrospective cohort study</td>
<td></td>
<td></td>
<td></td>
<td>OR 1.7,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p=0.012</td>
</tr>
<tr>
<td>Anis H, USA</td>
<td>12.541 -TKA</td>
<td>1 %</td>
<td>0.5 %</td>
<td>p=0.001</td>
</tr>
<tr>
<td>retrospective cohort study</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chiu FY et al, J Bone J Surg 2002
Gandhi R et al, J Arthroplasty 2009
Namba RS et al, J Arthroplasty 2009
Anis H et al, J Arthroplasty 2019
Prevention of deep infection in joint replacement surgery

DATA FROM META-ANALYSES (PHA)

<table>
<thead>
<tr>
<th>Citation</th>
<th>Lower</th>
<th>Upper</th>
<th>n (total)</th>
<th>p-value</th>
<th>Antibiotic</th>
<th>Non-antibiotic</th>
<th>Antibiotic cement</th>
<th>Non-antibiotic c.</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Espehaug (1997)</td>
<td>0.158</td>
<td>0.634</td>
<td>10905</td>
<td>0.001</td>
<td>11/6043</td>
<td>28/4862</td>
<td></td>
<td></td>
<td>0.316</td>
</tr>
<tr>
<td>Josefsson (1990)</td>
<td>0.178</td>
<td>1.038</td>
<td>1409</td>
<td>0.053</td>
<td>7/711</td>
<td>16/698</td>
<td></td>
<td></td>
<td>0.430</td>
</tr>
<tr>
<td>Josefsson (1993)</td>
<td>0.290</td>
<td>1.564</td>
<td>1115</td>
<td>0.36</td>
<td>9/565</td>
<td>13/550</td>
<td></td>
<td></td>
<td>0.674</td>
</tr>
<tr>
<td>Liebermann (1994)</td>
<td>0.168</td>
<td>16.908</td>
<td>35</td>
<td>0.65</td>
<td>2/19</td>
<td>1/16</td>
<td></td>
<td></td>
<td>1.684</td>
</tr>
<tr>
<td>Lynch (1987)</td>
<td>0.020</td>
<td>1.779</td>
<td>303</td>
<td>0.10</td>
<td>1/194</td>
<td>3/109</td>
<td></td>
<td></td>
<td>0.187</td>
</tr>
<tr>
<td>Lynch (1987)</td>
<td>0.382</td>
<td>2.501</td>
<td>1075</td>
<td>0.96</td>
<td>7/424</td>
<td>11/651</td>
<td></td>
<td></td>
<td>0.977</td>
</tr>
<tr>
<td>McQueen (1987)</td>
<td>0.047</td>
<td>5.567</td>
<td>295</td>
<td>0.57</td>
<td>1/146</td>
<td>2/149</td>
<td></td>
<td></td>
<td>0.510</td>
</tr>
<tr>
<td>Random combined</td>
<td>0.341</td>
<td>0.751</td>
<td>15127</td>
<td>0.001</td>
<td>38/8102</td>
<td>74/7035</td>
<td></td>
<td></td>
<td>0.506</td>
</tr>
</tbody>
</table>

Infection rate: 50 % lower in ALBC (deep infections: 1.2 vs 2.3 %, p=0.001)

RR of revision: 0.72

• Retrospective study, before and after the use of commercially available antibiotic-loaded bone cement (ALBC), N=2518. **Decrease of PJI 57% after the use of ALBC.** Sanz-Ruiz P, J Arthroplasty 2017

• Systematic review and comparison of various prevention strategies

12 studies, 9 strategies, N=123,788, **THA**

- Best combination: **iv AP + ALBC + conventional ventilation of surgery room**
  
  OR: 0,13 (vs simple cement without iv AP)
  
  OR: 0,44 (vs simple cement with iv AP)

ANTIBIOTIC IMPREGNATED BONE CEMENT (AIBC) IN ARTHROPLASTY

Zheng H, BMJ Open 2014
**Prevention of deep infection in joint replacement surgery**

**DATA FROM META-ANALYSES (PHA and PKA)**

A Systematic Review and Meta-Analysis of Antibiotic-Impregnated Bone Cement Use in Primary Total Hip or Knee Arthroplasty

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antibiotic Cement</th>
<th>Control</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>1.3.1 Hip</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Josefsson 1981</td>
<td>3</td>
<td>821</td>
<td>13</td>
</tr>
<tr>
<td>Pfarr 1979</td>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Wannske 1979</td>
<td>3</td>
<td>274</td>
<td>12</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>6</td>
<td>1195</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Tau² = 0.00; Chisq = 0.06, df = 1 (P = 0.81); I² = 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 3.51 (P = 0.0005)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.3.2 Knee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiu 2002</td>
<td>0</td>
<td>178</td>
<td>5</td>
</tr>
<tr>
<td>Hinarejos 2013</td>
<td>20</td>
<td>1483</td>
<td>20</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>20</td>
<td>1661</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Tau² = 2.11; Chisq = 2.86, df = 1 (P = 0.09); I² = 65%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 0.71 (P = 0.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.3.3 Hip and Knee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McQueen 1987</td>
<td>1</td>
<td>146</td>
<td>2</td>
</tr>
<tr>
<td>McQueen 1990</td>
<td>2</td>
<td>201</td>
<td>2</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>3</td>
<td>347</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Tau² = 0.00; Chisq = 0.18, df = 1 (P = 0.67); I² = 0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 0.35 (P = 0.72)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>3203</td>
<td>3090</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Total events</td>
<td>29</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Heterogeneity: Tau² = 0.53; Chisq = 10.54, df = 5 (P = 0.06); I² = 53%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect: Z = 2.03 (P = 0.04)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for subgroup differences: Chisq = 2.25, df = 2 (P = 0.32); I² = 11.2%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Significant differences in deep infection rate between the AIBC and control group (RR = 0.41; 95% CI, 0.17–0.97; P=0.04) BUT only for the hip

## Prevention of deep infection in joint replacement surgery

### DATA FROM META-ANALYSES (TKA)

<table>
<thead>
<tr>
<th>STUDY</th>
<th>No of TJA</th>
<th>ALBC Antibiotic –loaded Bone Cement Infection rate</th>
<th>Plain Cement Revision rate</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhou Y et al, 5 trials</td>
<td>6637</td>
<td>1.32</td>
<td>1.89</td>
<td>p=NS</td>
</tr>
<tr>
<td>Schiavone Panni A et al, 6 cohorts</td>
<td>6318</td>
<td></td>
<td></td>
<td>p=NS</td>
</tr>
<tr>
<td>Total deep infection rate: 1.55%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kleppel D et al, 11 articles (9 primary)</td>
<td>4092</td>
<td>1.16 % primary TKA</td>
<td>1.81 % revision TKA</td>
<td>7.93 %</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td></td>
<td>P= 0.006</td>
</tr>
</tbody>
</table>

Zhou Y et al, Surg Infect 2015
Kleppel D et al, World J Orthop 2017
EVIDENCE FROM REGISTRIES, RANDOMIZED TRIALS AND META-ANALYSES

• Suggests a protective effect of antibiotic-loaded bone cement (ALBC) against infection
  - in hips
  - NOT (or only mild) in knees

• Possible explanation:
  - smaller amount of cement used in TKA (usually a thin layer)
  - smaller duration and concentration of local antibiotics after surgery

Bohm E et al, Clin Ortop Rel Res 2014
TO CEMENT OR NOT TO CEMENT  
WHAT SURGEONS DO  
(50 years of use !)

<table>
<thead>
<tr>
<th>REGISTRY</th>
<th>CEMENTED</th>
<th>CEMENTED + ANTIBIOTIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norwegian Knee Arthroplasty</td>
<td>87 %</td>
<td>93 %</td>
</tr>
<tr>
<td>Northwest England, Primary TKA</td>
<td>97.7 %</td>
<td>93.7 %</td>
</tr>
<tr>
<td>Australian National Joint Replacement Registry 2017</td>
<td></td>
<td></td>
</tr>
<tr>
<td><a href="https://aoanjrr.sahmri.com">https://aoanjrr.sahmri.com</a></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>96.3 % (TKA)</td>
<td>93.7 % (THA)</td>
</tr>
</tbody>
</table>

- Primary THA: mainly uncemented (USA) - > 50 % (UK)  
  ALBC commonly used elsewhere

- Primary TKA: mainly cemented worldwide

National Joint Registry (UK) 2018 Report  
Kuhn KD. Maitrise Orthop 2015  
Fillingham Y et al, J Arthroplasty 2019

The frequency of surgeon use ranged from 74 to 100% in TKA and from 91 to 100% for THA.
POSSIBLE DISADVANTAGES OF ANTIBIOTIC LOADED BONE CEMENT (ALBC)

• Decrease in the compressive and tensile strengths of bone cement (high dose ALBC)
• Bone cellular toxicity (osteoblasts)
• Disturbed elution (hand-made ALBC)
• Renal toxicity
• Risk of allergic reactions
• Development of antibiotic resistance (mutant selection window)
• Economic cost (commercial ALBC)

HAND (CUSTOM) – MADE CEMENTS

• Inhomogenous mixture can: - reduce mechanical stability up to 40 %
  - jeopardise Ab diffusion rate and synergy

• Especially when adding high dose of antibiotic (≥4 g / 40 g PMMA)

• No study has clinically validated this effect

• BUT Lower antibiotic dose in primary prophylaxis (≤ 2 g / 40 g PMMA)

Moran JM et al, Clin Orthop Rel Res 1979
De Luise M et al, Orthopedics 2004
Sultan AA et al, Ann Transl Med 2019
ANTIBIOTIC RELEASE OF GENTAMYCIN AFTER MANUAL AND INDUSTRIAL ADDITION OF THE DRUG

Kuhn KD et al, Maitrise Orthop 2016
TOXICITY

• In vitro:
  - High gentamicin concentration: may decrease ALP activity and total DNA of osteoblasts
  - High tobramycin concentration: decrease osteoblast replication
  - High vancomycin concentration: caused the death of osteoblast

Ter Boo GJ et al, Biomaterials 2015  Bistolfi A et al, Inter Schol Res Net 2011

In vivo:
  - Aminoglycosides may be detected in the serum (uncommon)
  - Rare cases of nephrotoxicity (high aminoglycoside doses in cement, spacers)

BUT: - systemic toxicity is unusual when low doses are used
  - allergic reactions are rare
  - monitoring of nephrotoxicity when aminoglycosides or vancomycin is used

Sultan A, Ann Transl Med 2019
RESISTANCE

• Local Ab concentrations must exceed MIC and NBC of possible pathogens
• Low dose of Abs (0.5-1 g) may result in subinhibitory concentrations leading to R
• Release of Abs from different PMMA cements may vary
• Cement surface: ideal for bacterial colonization

Norwegian Joint Replacement Registry:
  - Aminoglycoside resistance: 1993-97: 47 %
  - 2003-07: 68 %

Cement + AG: development of CNS R to gentamycin
BUT cement + tobra: no changes in infecting pathogen profile

Nevertheless, no direct evidence linking ALBC to bacterial resistance

Possible explanation:
Ab in ALBC
Lutro O et al, Adv Orthop 2014

Neut D et al, J Antimicr Chemother 2001
Hansen E et al, J Arthroplasty 2014
Sultan A, Ann Transl Med 2019
ANTIBIOTIC RELEASE FROM COMMERCIAL PMMA CEMENTS

Blue bars: content of Ab in cement powder %,
Green: overall release of Ab within 7 days %

Kuhn KD, PMMA Cement, Springer 2014
ALBC AND 2^{ND} STAGE REVISION SURGERY

- **Not always prophylaxis** (infection may persist!)

- **Higher dose Ab cement (2-4 g / 40 g cement powder)**
  - may become bactericidal in local bone environment e.g. clindamycin
  - more effective against biofilm e.g. G+C
  - may compromise mechanical stability

- **Vancomycin + gentamycin for MRSA/MRSE**: strong bactericidal effect and elution

- **Commercial ALBC**: homogenous mixture of matrix, stable antibiotic elution
  - BUT certain combinations inappropriate in certain MDR bacteria

- Fewer available studies

  Moran et al, Clin Orthop Rel Res 1979
  Kuhn KD, Maitrise Orthop 2016
COST AND COST-EFFECTIVENESS

- Cost of pre-mixed ALBC in TKA: 120,000 $ per prevented infection
  Gutowski CZ et al, Bone Joint J 2014
- Cost of infected TKA: MSSA 68,000 $, MRSA 107,000 $,
  Parvizi J, J Arthroplasty 2010
- If ABLC for 50% of 500,000 primary TJA + cost of PJI = 50,000 $ (total: 117,000,000)
  - the infection rate should be lowered from 1.5 % to 1.2 % to balance the cost
- Cost of ALBC for 100 primary TJA: 60,000 $ equal the cost of one PJI
  - to be cost-effective the infection rate should decrease 1 % (difficult !)
  Illingworth KO et al, J Bone Joint Surg Am 2013
- Perhaps cost-effective with hand-mixed cement: 2,112-37,176 $ per infection saved
- May be cost effective in young pts (<71) and when the cost of cement < 650 $
  Cummings JS et al, J Bone Joint Surg Am 2009

Is the increased cost sustainable when the efficacy of prevention is not fully established?
Sultan AA et al, Ann Transl Med 2019
GUIDELINES
WHAT THE GUIDELINES SUGGEST

Second International Consensus on Periprosthetic Joint Infection
July 25-27, 2018

Thomas Jefferson University, Philadelphia

and Fillingham Y et al, J Arthroplasty 2019
WHAT THE GUIDELINES SUGGEST

Question 1: Is there sufficient evidence to support the use of antibiotic-loaded cement in primary TKA or THA to reduce the risk of SSI/PJI?

RESEARCHED BY:

Yale Fillingham, MD
Sergei Oshkukov, MD
Ali Parsa, MD

Fillingham Y et al, J Arthroplasty 2019
Literature:

• Meta-analysis 1, Prospective/Randomized 0, Retrospective 26

• A number of retrospective studies have correlated use of antibiotic-loaded cement with lower rates of wound infection and failure in THA and TKA, whereas others show no difference

• **No evidence exists** demonstrating that use of antibiotic-loaded cement reduces incident of SSI/PJI in **primary hip or knee arthroplasty**
**Recommendation:** There is **no conclusive evidence** to demonstrate that routine use of antibiotic-loaded cement in primary TKA or THA reduces the risk of subsequent SSIs/PJIs. Recent high level evidence and registry data has not demonstrated a reduction in SSI/PJIs. Furthermore, the added cost, the potential for the emergence of resistant organisms and the potential adverse effect of antibiotics on the host provide adequate reasons **to refrain** from routine use of antibiotic loaded cement during primary total joint arthroplasty.

**Level of Evidence:** Moderate

A. Agree 38 %
B. Disagree 58 %
C. Abstain 4 %
WHAT THE GUIDELINES SUGGEST

Question 2: Is there a role for the use of antibiotic-impregnated cement in primary total joint arthroplasty?

RESEARCHED BY:

Yale Fillingham, MD
Sergei Oshkukov, MD
Ali Parsa, MD

Fillingham Y et al, J Arthroplasty 2019
Literature:

• Meta-analysis 1, Prospective/Randomized 0, Retrospective 26

• A number of retrospective studies have correlated use of antibiotic-loaded cement with lower rates of wound infection and failure in THA and TKA, whereas others show no difference.

• No evidence exists demonstrating that use of antibiotic-loaded cement reduces incident of SSI/PJI in primary hip or knee arthroplasty.
**Recommendation:** Antibiotic-impregnated cement *may be used* during primary TJA to reduce the risk of surgical site infections /periprosthetic joint infections (SSIs/PJIs).

The benefits of antibiotic-impregnated cement versus its cost and other potential adverse effects, may be most justified in patients at high risk of infection (eg. diabetes, immunosuppression)

**Level of Evidence:** Moderate

- A. Agree
- B. Disagree
- C. Abstain
Q2-2 Can topical use of antimicrobials or antimicrobials attached to the surface of foreign bodies (e.g. intravenous lines, urinary catheters, trachealtubes, artificial joints, bone cements for orthopaedic surgery) be used to prevent some (which?) biofilm infections? Can the risk period be defined?

There is good evidence to suggest that antibiotic-impregnated materials (frequently gentamicin but also tobramycin and vancomycin) reduce the incidence of prosthesis-associated biofilm infections (AI).

Hoiby N et al, Clin Microb Infect 2015
Q20. What are the most effective strategies to reduce the risk of biofilm formation and SSI in prosthetic joint arthroplasty patients?

Q20A. How effective are cement modifications

Q20. Recommendations
20A. Available evidence suggests uncertain tradeoffs between the benefits and harms regarding cement modifications and the prevention of biofilm formation or SSI in prosthetic joint arthroplasty. (No recommendation/unresolved issue)

Berrios-Torres S et al, JAMA Surgery 2017
FDA has approved premixed aminoglycoside (i.e., gentamicin and tobramycin) in bone cement products for use in hip, knee, or other joints in second-stage revision of total joint arthroplasty. The products are not approved for prophylaxis in primary joint replacement procedures.

While antimicrobial bone cement has not been shown to be superior to i.v. antimicrobials, there is evidence that supports the combination of using antimicrobial-laden bone cement together with systemic antimicrobial prophylaxis.
The use of low-dose antimicrobial-laden fixation cement for prevention of infection in primary cemented hip and knee arthroplasty (in conjunction with intravenous antimicrobial prophylaxis) is common practice.

The optimal use of this strategy and the potential for the development of resistance has not been fully assessed;

It may be appropriate in selected patients at increased risk for infection e.g. diabetes, immunosuppression
CONCLUSIONS

• The use of ALBC in primary THA and TKA is still controversial

• Question concerning:
  - efficacy (especially TKA)
    - mechanical stability
    - antibiotic resistance
    - cost-effectiveness

• Nevertheless, still widely used

• Always with systemic prophylactic antibiotics

• Lack of large randomized clinical trials
Thank You
BACK UP SLIDES
Significant differences in deep infection rate between the AIBC and control group (RR = 0.41; 95% CI, 0.17–0.97; P=0.04)

Prevention of deep infection in joint replacement surgery

Figure 3. Prosthesis survival with revision due to infection as endpoint following 45,250 primary total hip replacements, performed in Norway in 1987–2007, where no antibiotic prophylaxis (None), intravenous antibiotic prophylaxis (S), antibiotic-impregnated cement (C), or both intravenous antibiotic prophylaxis and antibiotic-impregnated cement (SC) was used. 2,137 operations were performed in a clean-air enclosure, 21,627 in operating theaters with laminar flow, and the remaining operations in operating theaters with standard air ventilation.

Jamsen E, Acta Orthop 2010
META-ANALYSIS OF ANTIBIOTIC IMPREGNATED BONE CEMENT (AIBC) IN ARTHROPLASTY

- 8 RCTs, N=6138 arthroplasties (3217 AIBC, 3101 controls)
- AIBC significantly decreased deep infection rate (RR 0.41, 95CI: 0.17-0.97) after primary THA/TKA compared to bone cement or AP alone
- No advantage for superficial infection
- Gentamycin superior to cefuroxime (p=0.0005)

Figure 3. The RRs and 95% CIs for the incidence of deep infection among patients treated with vs. without antibiotic bone cement. (ALBC vs. PBC and ALBC vs. SA) [ALBC: antibiotic-loaded bone cement; PBC: plain bone cement; SA: systemic antibiotic].
TOPICAL ANTIBIOTICS AS PROPHYLAXIS

YES!

- Considerable evidence to support the use of antibiotic-impregnated bone cement as AP in TJR (THA, TKA) in addition to iv antibiotics (SIGN, evidence level 2)
- Data also derived from registry-based studies (Scandinavia, France, Australia)
- Meta-analysis (n=36,033 THA): 50 % decrease in SSI rates (2.3 % to 1.2 %) 
  

- No evidence to support the concept of adverse effects on mechanical properties, development of resistance or toxicity
- Evidence for effectiveness in closed (but not in open) fractures
- ALBC is currently used as routine AP in Scandinavian countries and many centres in Europe

Bratzler DW, ASHP Report, Am J Health Syst Pharm 2013
Parvizi J, Gehrke T. International Consensus Meeting on PJI 2013
Shuman EK, Drug Aging 2011
McHugh JM, JAC 2011
Scottish Intercollegiate Guidelines Network 2009
Hanssen AD, Clin Orthop Related Res 1999
Jamsen E, Acta Orthop 2010
Jiranek WA, JBJS 2006

Saeed K, IJAA 2017
Jamsen E, Acta Orthop 2010
Matar WY, JBJS Am 2010
Meehan J, JBJS Am 2009
Hansen EN, J Arthroplasty 2014
Roberts DW, JBJS Am 2013
TOPICAL ANTIBIOTICS AS PROPHYLAXIS

YES?

- Small RCTs with conflicting results
- The use of collagen sponges with gentamycin do not prevent PJI
- FDA: approval of premixed Ab bone cement (genta, tobra) as AP in 2\textsuperscript{nd} stage reimplantation following a previous infection, but not in primary TJA
- Many use it in revision arthroplasty or in patients with high-risk operations, eg DM
- Large prospective RCTs needed – But perhaps not feasible for practical, statistical and ethical reasons
- Questions concerning resistance, allergy, toxicity, cost and prosthesis stability

Bratzler DW, ASHP Report, Am J Health Syst Pharm 2013
Parvizi J, Gehrke T. International Consensus Meeting on PJI 2013
Saed K, IJAA 2017
Westberg M, CID 2015
Shuman EK, Drug Aging 2011
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Matar WY, JBJS Am 2010
Scottish Intercollegiate Guidelines Network 2009
ASHP 2010
Hanssen AD, Clin Orthop Related Res 1999
Meehan J, JBJS Am 2009
Jamsen E, Acta Orthop 2010
Hansen EN, J Arthroplasty 2014
Jiranek WA, JBJS 2006
Roberts DW, JBJS Am 2013
## Local Antimicrobials in Bone Cement (PMMA)

(Supportive to surgical and systemic antimicrobial treatment)

<table>
<thead>
<tr>
<th>Standard regimen (incl. culture negative)</th>
<th>Antimicrobial (AM)</th>
<th>Fixation: prophylactic use</th>
<th>Spacer: therapeutic use (combinations of 2 or 3 AM up to 4g per 40g industrial impregnated PMMA cement)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gentamicin + Clindamycin</td>
<td>1 g</td>
<td>1 g + Vancomycin 2-4 g</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative regimen</th>
<th>Gentamicin + Vancomycin</th>
<th>0.5 g</th>
<th>0.5 g</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Staphylococcus spp.</strong> (oxacillin/methicillin-resistant) and Enterococcus spp.</td>
<td>Gentamicin + Linezolid or Daptomycin or Fosfomycin</td>
<td>0.5 g 2 g 1 g</td>
<td>0.5 g 2 g 1 g</td>
</tr>
<tr>
<td><strong>Other resistant gram-positive pathogens (e.g. VRE)</strong></td>
<td>Gentamicin + Colistin (Natrum Sulfat) or Fosfomycin (Trometamol) or Meropenem or Ciprofloxacin</td>
<td>0.5 g 2 g (≈ 60 Mio E) 1 g 2 g 2 g</td>
<td>0.5 g 2 g (≈ 60 Mio E) 1 g 2 g 2 g</td>
</tr>
<tr>
<td><strong>Resistant gram-negative pathogens (e.g. Klebsiella spp., Pseudomonas spp., Acinetobacter spp., Proteus spp., E. coli spp.)</strong></td>
<td>Gentamicin + Amphotericin B liposomal (AmBisome®)</td>
<td>0.5 g 0.1 g active substances (corresp. to 2 amp. of 1.33 g substances as is = 2.66 g added AM)</td>
<td>Not yet determined</td>
</tr>
<tr>
<td><strong>Candida spp. (e.g. Candida albicans, Candida parapsilosis)</strong></td>
<td>Gentamicin + Voriconazole (Rotexmedica®)</td>
<td>0.5 g 0.2 g active substances (corresp. to 1 amp. of 3.5 g substances as is)</td>
<td>Not yet determined</td>
</tr>
</tbody>
</table>

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C. Berberich, Workshop PJI, Pro-Implant Foundation, April 10, 2018
Antibiotic Prophylaxis in Surgery

It is well established that the administration of systemic antibiotics immediately before surgery (perioperatively) significantly reduces the incidence of postoperative Surgical Site Infections in all surgical categories.

CDC USA 1999, British Orthopaedic Association (BOA) 2006
National Institute of Clinical Excellence (NICE) 2008
National Health and Medical Research Council (NHMRC, Australia) 2010
Merollini K, Am J Infect Control 2013

However, it must always be remembered that Antibiotic Prophylaxis is not a Substitute for Good Surgery.

Sia A, Infect Dis Clin N Amer 2005