HOW TO REDUCE EFFICIENTLY POST-OPERATIVE INFECTIONS?

PROPHYLACTIC ANTIBIOTIC USE IN ORTHOPAEDIC SURGERY

Antonios Papadopoulos
Assistant Professor in Internal Medicine and Infectious Diseases
Athens Medical School - University Hospital ATTIKON
Infectious complications are the main cause of morbidity and mortality in surgery.

Every operation in surgery is an experiment in bacteriology

Moynihan BGA, Br J Surg 1920
# SURGICAL SITE INFECTIONS (SSIs) – USA 2006-2008

<table>
<thead>
<tr>
<th>Risk category</th>
<th>Per 100 procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal fusion</td>
<td>0.7-4.15</td>
</tr>
<tr>
<td>Laminectomy</td>
<td>0.7-2.3</td>
</tr>
<tr>
<td>Hip prosthesis</td>
<td>0.6-2.4</td>
</tr>
<tr>
<td>Knee prosthesis</td>
<td>0.5-1.6</td>
</tr>
</tbody>
</table>

INFECTION PREVENTION MEASURES

- Risk factor correction (Diabetes, Ca, immunosuppression, poor nutrition, hypoalbuminemia, 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 impregnated cement

ANTIBIOTIC CHEMOPROPHYLAXIS

Mohajer MA & Darouiche RO, J Appl Biomater Funct Mater 2014
There is no evidence that antibiotics will hinder infections caused by poor surgery.
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
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
Goals and Principles of Antibiotic Prophylaxis

- To reduce morbidity and mortality
- To prevent bacterial resistance on normal floras in particular, and,
- To reduce the duration of hospital stay and the cost of health care
- To reduce the incidence of adverse effects.

Bratzler DW, ASHP Report, Am J Health Syst Pharm 2013
Merollini K, Am J Infect Control 2013
CHEMOPROFYLAXIS IN ORTHOPAEDICS

- DECREASED INFECTION RATE

- after total hip or knee replacement therapy 81%
  Meta-analysis of 26 RCTs Al Buhairan B, JBJS Br 2008

- after closed fracture osteosynthesis 80%

- after open fracture osteosynthesis 78%

- After spinal surgery 63%

No efficacy data for shoulder, elbow and ankle TJR

Walenkamp G, EFORT, 2001
Brown EM, Spine 2004
Matar WY, JBJS Am 2010

Southwell-Kelly JP, Clin Orthop Rel Res 2004
Norden CM, Rev Infect Dis 1983
When to be Administered?

It is at least inappropriate to apply antibiotics

too early ... … or too late!
THE TIMING OF PROPHYLACTIC ADMINISTRATION OF ANTIMICROBIALS AND THE RISK OF SURGICAL WOUND INFECTION

<table>
<thead>
<tr>
<th>Timing of administration</th>
<th>Incidence of surgical wound infections in 2847 pts</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early administration (369 pts) (2-24h before incision)</td>
<td>3.8% (p&lt;0.0001)</td>
<td>4.3</td>
</tr>
<tr>
<td>Preoperative (1708 pts) (2h before)</td>
<td>0.6%</td>
<td>1</td>
</tr>
<tr>
<td>Perioperative (282 pts) (0-3h after)</td>
<td>1.4% (p=0.12)</td>
<td>2.1</td>
</tr>
<tr>
<td>Postoperative (488 pts) (&gt;3h - &lt;24h)</td>
<td>3.3% (p&lt;0.0001)</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Goals and Principles of Antibiotic Prophylaxis

When to be Administered?

- The administration of the drug within 60 min before surgical incision is safe and effective and perhaps the most important factor.

- The risk of SSI increases 2- to 6-fold when AP is given too early or too late, i.e., > 2 hours prior to or > 2 hours after the initial incision respectively.

Van Kasteren ME, CID 2007
Steinberg JP, Ann Surg 2009
Bratzler DW, ASHP Report, Am J Health Syst Pharm 2013
SURGICAL SITE INFECTION RATE ACCORDING TO TIME OF PROPHYLAXIS

Burke JB. Clin Infect Dis 2001; 33(Suppl 2): S78-83
Surgical site infection risk based on timing of perioperative antibiotic dose. Annotation shows number of infections/number of operations for each time interval.

Steinberg JP, Ann Surg 2009
OPTIMAL TIMING OF ANTIMICROBIAL PROPHYLAXIS (AP)
A randomized controlled trial

Evaluating the optimal timing of surgical antimicrobial prophylaxis: study protocol for a randomized controlled trial

Edin Mujagic¹, Tibor Zwimpfer¹, Walters P Marti², Marcel Zwahlen³, Henry Hoffmann¹, Christoph Kindler⁴, Christoph Fux⁵, Heidi Misteli⁶, Lukas Iselin¹, Andrea Kopp Lugli⁵, Christian A Nebiker⁴, Urs von Holzen¹, Fabrizio Vinzens¹, Marco von Strauss², Stefan Reck³, Marko Kraljevic¹, Andreas F Widmer², Daniel Oertli¹, Rachel Rosenthal and Walter P Weber¹

Switzerland, N= 5,000 pts
Various surgical procedures
AP 30-75 min vs < 30 min before incision

Mujagic E, Trials 2014
The optimal timing of antibiotic administration is
1) within 60 minutes prior to incision and
2) within 2 hours if vancomycin (or FQs) is indicated (due to extended infusion time and possible red neck syndrome)
Goals and Principles of Antibiotic Prophylaxis

Whenever a proximal tourniquet is required, the entire antimicrobial dose should be administered before the tourniquet is inflated.

AAOS 2004 Meehan J, JBJS Am 2009
Bratzler DW, ASHP Report, Am J Health Syst Pharm 2013
TOTAL KNEE ARTHROPLASTY – AP AFTER INCISION

- Double blind RCT, n=908
- AP (cefuroxime) before tourniquet inflation vs 10 min prior tourniquet release
- No difference in deep-tissue infection between groups
- These data suggest that administering AP after obtaining intraoperative cultures and before tourniquet release is reasonable for patients undergoing 2nd stage replacement arthroplasty

Soriano A, CID 2008
# Antibiotic Prophylaxis in Open Fractures

<table>
<thead>
<tr>
<th>Grade</th>
<th>AP Administration</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 and 2</td>
<td>Upon admission and/or prior to surgery</td>
<td>24 hours</td>
</tr>
<tr>
<td>3</td>
<td>Upon admission (preemptive empirical therapy)</td>
<td>3-5 days</td>
</tr>
</tbody>
</table>

Vogt M, Uçkay I, Bodler P. In: Infections of the musculoskeletal system 2014
ANTIBIOTIC PROPHYLAXIS IS NOT RECOMMENDED

- Arthroscopic procedures (without instrumentation)
- Arthrotomy
- Amputations (if not infection induced)
- Removal of osteosynthesis material

Vogt M, Uşkay I, Bodler P. In: Infections of the musculoskeletal system 2014
A single prophylactic dose is normally sufficient and postoperative doses are usually unnecessary and should not be given.

In any case, not beyond 24 hours

Prolonged AP: toxicity, resistance, cost
OPTIMAL DURATION OF ANTIMICROBIAL PROPHYLAXIS

- Prospective double-blinded multicenter study, N=1354
- 1-day cefuroxime vs 3-day cefazolin
- Prevalence of wound infection: - THA 0.5 % vs 1.2 %
- - TKA 0.6 % vs 1.4 %
  Mauerhan DR, JBJS Am 1994

- AP in THA / TKA, N=466
- 1-day vs 7-day AP of nafcillin or cefazoline
- 1 dose vs 2-day AP of nafcillin or cefazoline
- No difference in infection prevalence
  Haydemann JS, Clin Orthop Rel Res 1986
How Many Doses?

- If the antimicrobial agent has a short half-life and the duration of the operation is more than 2-4 hours (T1/2 >x2) or
- if there is major blood loss during the operation (e.g. > 1500 ml),
- then additional doses of the drug are justified during the procedure, but for less than 24 hours.

Matar WY, JBJS Am 2010
Scottish Intercollegiate Guidelines Network 2009
DURATION OF AP – DRAINS / CATHETERS

Medical literature:

- Does not support the continuation of AP until all drains or catheters are removed

AAOS 2004 (18 references)          Matar WY, JBJS Am 2010
Bratzler DW, ASHP Report, Am J Health Syst Pharm 2013
MOST LIKELY PATHOGENS

- Staph. aureus (MSSA-MRSA)
- Coagulase negative staphylococci (CNS)
- Streptococci, enterococci
- GRAM negatives

CDC, Infect Contr Hosp Epidem 1999
Matar WY, JBJS Am, 2010
PERI OPERATIVE ANTIBIOTIC PROPHYLAXIS
## RECOMMENDATIONS FOR ORTHOPAEDIC ANTIMICROBIAL PROPHYLAXIS

<table>
<thead>
<tr>
<th>TYPE OF PROCEDURE</th>
<th>RECOMMENDED AGENT</th>
<th>ALTERNATIVE AGENTS</th>
<th>STRENGTH OF EVIDENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean (no device implantation)</td>
<td>None</td>
<td>None</td>
<td>C</td>
</tr>
<tr>
<td>Spinal ± instrumentation</td>
<td>Cefazolin</td>
<td>Vancomycin, Teicoplanin, Clindamycin</td>
<td>A</td>
</tr>
<tr>
<td>Hip fracture repair</td>
<td>Cefazolin</td>
<td>Vancomycin, Teicoplanin, Clindamycin</td>
<td>A</td>
</tr>
<tr>
<td>Internal fixation (screws, nails, plates, wires)</td>
<td>Cefazolin</td>
<td>Vancomycin, Teicoplanin, Clindamycin</td>
<td>A</td>
</tr>
<tr>
<td>Total joint replacement</td>
<td>Cefazolin</td>
<td>Vancomycin, Teicoplanin, Clindamycin</td>
<td>A</td>
</tr>
</tbody>
</table>

Bratzler DW, ASHP Report, Am J Health Syst Pharm 2013
Parvizi J, Gehrke T. International Consensus Meeting on PJI 2013
The Choice of Antibiotic in Orthopaedic Surgical Prophylaxis

In case that local predominance of MRSA permits (<15% prevalence) then:

- A 2nd generation Cephalosporin could also be given:
  - Cefuroxime 1.5g iv
  - Ceforanide 2g iv

- In case of allergy, Clindamycin or Vancomycin or Teicoplanin can be used.
<table>
<thead>
<tr>
<th>AGENT</th>
<th>DOSE</th>
<th>HALF-LIFE (h)</th>
<th>INFUSION DURATION (min)</th>
<th>REDOSING INTERVAL (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>1 gr iv (&lt;60-80 kg)</td>
<td>1.2-2.5</td>
<td>3-5</td>
<td>4 (2-5)</td>
</tr>
<tr>
<td></td>
<td>2 gr iv (&gt;60-80 kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>750 mg iv (&lt;80 kg)</td>
<td>1-2</td>
<td>3-5</td>
<td>3-4</td>
</tr>
<tr>
<td></td>
<td>1.5 g iv (&gt;80 kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1 gr iv (15 mg/kg)</td>
<td>4-6</td>
<td>60</td>
<td>6-12</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>400-800 mg iv</td>
<td>40 -&gt;100</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8-10 mg/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>600-900 mg iv</td>
<td>2-5</td>
<td>10-60</td>
<td>3-6</td>
</tr>
</tbody>
</table>

Dose adjustments in obese pts

Bratzler DW, ASHP Report, Am J Health Syst Pharm 2013
Parvizi J, Gehrke T. International Consensus Meeting on PJI 2013
Hansen E, J Arthroplasty 2014

AAOS 2004
Shuman E, Drugs Aging 2011
Treat Guidel Med Lett 2006
Periti P, Eur J Clin Microbiol Infect 1999
CEPHALOSPORINS

1st GENER.: Cefazolin
2nd GENER.: Cefuroxime, cefamandole etc

- Bactericidal activity against staphylococci (NOT MRSA/MRSE), streptococci and some Gram negatives
- Favorable toxicity profile – allergy possible
- Good and rapid penetration into soft tissue and bone
- Low cost

Bratzler DW, ASHP Report, Am J Health Syst Pharm 2013
Parvizi J, Gehrke T. International Consensus Meeting on PJI 2013
Shuman E, Drug Aging 2011
Hill C, Lancet 1981
Penetration of Antibacterials into Bone
Pharmacokinetic, Pharmacodynamic and Bioanalytical Considerations

Cornelia B. Ladersdorfer,1 Jürgen B. Bulitta,1 Martina Kinzig,1 Ulrike Hotzgrabe2 and Fritz Schmitz1

1 BMB-Institute for Biomedical and Pharmaceutical Research, Nürnberg-Henndelberg, Germany
2 Institute of Pharmacy and Food Chemistry, University of Würzburg, Würzburg, Germany
3 Department of Pharmacology, University of Duisburg-Essen, Essen, Germany

Clinical Pharmacotherapy 2009
GLYCOPEPTIDES

VANCOMYCIN

- Activity against staphylococci (PLUS MRSA/MRSE), streptococci and enterococci
- Lack of activity against Gram negatives
- Variable penetration into bone
- Prolonged infusion
- Potential for systematic toxicity

TEICOPLANIN

- RCT: 1 dose comparable to 5 doses/d of cefazolin
  AEs: teicho 0.7 % vs cefazolin 2.1 % (p=0.08)
- Long T1/2, low toxicity

Shuman E, Drug Aging 2011
Periti P, Eur J Clin Microbiol Infect 1999
Wood MJ, AAC 1996
VANCOMYCIN VS CEPHALOSPORIN

- Limited data

- Prospective randomized data, Patras, n=435 (THA 260, TKA 175)
  - cefuroxime vs vancomycin vs fusidic acid
  - No difference in the rate of PJI between groups
  - institution with MRSA/MRSE >25 %
  - main limitation: low power to detect meaningful differences

Tyllianakis M, J Arthroplasty 2010
Is it Time to Include Vancomycin for Routine Perioperative Antibiotic Prophylaxis in Total Joint Arthroplasty Patients?

Eric B. Smith, MD, Rachael Wynne, RN, Ashish Joshi, MD, MPH, Hans Liu, MD, and Robert K. Good, MD

**Fig. 1.** Infection (PJI) rate 2006 to 2010. There was a statistically significant reduction in PJI after June 1, 2008 with initiation of vancomycin for perioperative prophylaxis of primary THA and TKA. The overall PJI rate reduced from 1.0% before June 1, 2008, to 0.5% ($P = .03$) after.
SELECTION OF AGENTS IN ANTIBIOTIC PROPHYLAXIS IN TJR

- No data supporting superiority of one class of antibiotic over another
- Meta-analysis (in settings and time with low MRSA prevalence)
  **NO difference** between:
  - cephalosporin vs teicoplanin (5 studies, THA, TKA, n=2625)
  - cephalosporin vs penicillin-derivative (3 studies, THA, TKA, n=386)
  - 1st vs 2nd generation cephalosporins (8 studies, THA, TKA, n=2879)
- Selection should be based on: - cost – availability
  - local resistance patterns
  - patient's history and characteristics
- Same principles should be applied for shoulder arthroplasty

Bratzler DW, ASHP Report, Am J Health Syst Pharm 2013
Al Buhairan B, JBJS Br 2008
MRSA increase in PJI

1999 27 %
2006 62 %

Parvisi J, Instr Course Lect 2009

Percentages represent the portion of total new cases that were CA-MRSA.

(*This figure represents the portion of CA-MRSA found during a 6-month survey in 2005.
**This figure represents the CA-MRSA found during an 8-month survey in 2007.)
Causative organisms in revision total hip & knee arthroplasty for infection: Increasing multidrug antibiotic resistance in coagulase-negative Staphylococcus and the implications for antibiotic prophylaxis

A.M. Malhas a, R. Lawton a, M. Reddy b, D. Nathwani b, R.A. Clift a

a Department of Trauma and Orthopaedics, Ward 1B/19, Ninewells Hospital, NHS Tayside, Dundee, Scotland DD2 1UB, UK
b Department of Infectious Disease, Ward 1B/19, Ninewells Hospital, NHS Tayside, Dundee, Scotland DD2 1UB, UK

Methicillin resistance of SA & CNS arthroplasty infections, MR = resistant, MS = sensitive.
Proportion of Methicillin resistant Staphylococcus aureus (MRSA) isolates in participating countries in 2010

<table>
<thead>
<tr>
<th>Country</th>
<th>MRSA</th>
<th>VREF</th>
<th>VREFM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>32.3</td>
<td>0.0</td>
<td>6.4</td>
</tr>
<tr>
<td>France</td>
<td>27.7</td>
<td>0.3</td>
<td>3.6</td>
</tr>
<tr>
<td>Germany</td>
<td>15.4</td>
<td>1.1</td>
<td>27.0</td>
</tr>
<tr>
<td>Greece</td>
<td>50.1</td>
<td>4.9</td>
<td>36.8</td>
</tr>
<tr>
<td>Ireland</td>
<td>46.1</td>
<td>1.9</td>
<td>62.4</td>
</tr>
<tr>
<td>Israel</td>
<td>42.4</td>
<td>3.0</td>
<td>21.8</td>
</tr>
<tr>
<td>Italy</td>
<td>30.8</td>
<td>2.9</td>
<td>19.2</td>
</tr>
<tr>
<td>Poland</td>
<td>29.0</td>
<td>5.8</td>
<td>33.7</td>
</tr>
<tr>
<td>Portugal</td>
<td>61.3</td>
<td>0.0</td>
<td>4.4</td>
</tr>
<tr>
<td>Russia</td>
<td>28.3</td>
<td>14.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Spain</td>
<td>22.8</td>
<td>0.0</td>
<td>2.9</td>
</tr>
<tr>
<td>Sweden</td>
<td>1.3</td>
<td>0.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Switzerland</td>
<td>14.2</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Turkey</td>
<td>27.0</td>
<td>0.0</td>
<td>22.4</td>
</tr>
<tr>
<td>UK</td>
<td>37.8</td>
<td>9.3</td>
<td>44.2</td>
</tr>
<tr>
<td>Overall</td>
<td>27.2</td>
<td>1.6</td>
<td>24.7</td>
</tr>
</tbody>
</table>

Sader HS, J Chemotherapy 2011
<table>
<thead>
<tr>
<th>Hospital</th>
<th>% MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>GR001</td>
<td>3.8%</td>
</tr>
<tr>
<td>GR004</td>
<td>2.8%</td>
</tr>
<tr>
<td>GR005</td>
<td>3.0%</td>
</tr>
<tr>
<td>GR007</td>
<td>14.8%</td>
</tr>
<tr>
<td>GR009</td>
<td>7.2%</td>
</tr>
<tr>
<td>GR010*</td>
<td>11.7%</td>
</tr>
<tr>
<td>GR011*</td>
<td>10.4%</td>
</tr>
<tr>
<td>GR013</td>
<td>6.4%</td>
</tr>
<tr>
<td>GR014</td>
<td>8.8%</td>
</tr>
<tr>
<td>GR015</td>
<td>8.6%</td>
</tr>
<tr>
<td>GR018</td>
<td>9.5%</td>
</tr>
<tr>
<td>GR024</td>
<td>9.5%</td>
</tr>
<tr>
<td>GR026</td>
<td>7.8%</td>
</tr>
<tr>
<td>GR027</td>
<td>3.7%</td>
</tr>
<tr>
<td>GR028</td>
<td>5.6%</td>
</tr>
<tr>
<td>GR030</td>
<td>5.9%</td>
</tr>
<tr>
<td>GR031</td>
<td>4.0%</td>
</tr>
<tr>
<td>GR032</td>
<td>3.1%</td>
</tr>
<tr>
<td>GR033</td>
<td>2.2%</td>
</tr>
<tr>
<td>GR035</td>
<td>6.6%</td>
</tr>
<tr>
<td>GR037</td>
<td>4.8%</td>
</tr>
<tr>
<td>GR038</td>
<td>1.9%</td>
</tr>
<tr>
<td>GR039</td>
<td>3.9%</td>
</tr>
<tr>
<td>GR040</td>
<td>7.0%</td>
</tr>
<tr>
<td>GR041</td>
<td>16.2%</td>
</tr>
<tr>
<td>GR043</td>
<td>8.7%</td>
</tr>
<tr>
<td>GR047</td>
<td>8.0%</td>
</tr>
<tr>
<td>GR048</td>
<td>1.0%</td>
</tr>
<tr>
<td>GR049</td>
<td>3.4%</td>
</tr>
<tr>
<td>GR050</td>
<td>5.1%</td>
</tr>
<tr>
<td>GR051</td>
<td>8.5%</td>
</tr>
<tr>
<td>GR055</td>
<td>3.4%</td>
</tr>
<tr>
<td>GR057*</td>
<td>10.5%</td>
</tr>
<tr>
<td>GR060</td>
<td>5.1%</td>
</tr>
<tr>
<td>GR062</td>
<td>5.0%</td>
</tr>
<tr>
<td>GR064</td>
<td>9.1%</td>
</tr>
<tr>
<td>GR068</td>
<td>2.6%</td>
</tr>
<tr>
<td>GR070</td>
<td>8.7%</td>
</tr>
<tr>
<td>GR071</td>
<td>3.7%</td>
</tr>
<tr>
<td>GR075</td>
<td>3.9%</td>
</tr>
</tbody>
</table>

**Weighted Average**

- 6.8%
- 363
- 36.8
- 36.7
- 0.1
- 8.7%
- 955
- 40.2
- 40.0
- 0.2
- 2.9%
- 264
- 45.1
- 45.1
- 0.0

**Hospital Mean**

- 36%
- 36.2
- 0.1
- 39.1
- 39.0
- 0.1
- 43.3
- 43.3
- 0.0

40 Greek Hospitals: medical wards MRSA mean 36%
surgical wards 40% (11-73%)
ICU 43%
SSIs AND RESISTANCE

- ??, Chicago (hospitals): susceptibility to cefazolin 44 and 74 %
- Resistance to standard AP: 26-56 %
- Resistance of CNS and S.aureus to cefazolin: 75 % and 30 %
- All sensitive to vancomycin
- UK: resistance to cefuroxime (AP): 29 %

Fulkerson E, JBJS Am 2006
Routine use of Vancomycin for prophylaxis should be discouraged because it promotes emergence of Vancomycin-Resistant Organisms: VRE, VISA, hVISA, VRSA.

Vancomycin is inferior against MSSA compared to cephalosporin and penicillinase-resistant penicillin.

May promote the development of MSSA SSIs.

Bratzler DW, ASHP Report, Am J Health Syst Pharm 2013
Parvizi J, Gehrke T. International Consensus Meeting on PJI 2013
Bull AL, Ann Surg 2012
VANCOMYCIN AS ANTIBIOTIC PROPHYLAXIS (AP)

- Vancomycin provides effective prophylaxis in high risk patients

- It has not been demonstrated that the use of vancomycin as AP is associated with resistance emergence

- The choice of the antibiotic is based on the epidemiological knowledge of the literature and the experience on the ward

Meehan J, JBJS Am 2009
Savarese A, Chir Organi Mov 1999
VANCOMYCIN USE

• Increasing CA-MRSA and Hospital Aquired (HA)-MRSA

• Some use vancomycin plus cefazolin as AP in settings with high MRSA/MRSE prevalence or SSIs with both MSSA & MRSA

• No consensus about what constitutes a high prevalence of methicillin resistance

• Role of vancomycin vs cefazolin in high MRSA prevalence - inconclusive data and conflicting results

• RCTs are lacking

Bratzler DW, ASHP Report, Am J Health Syst Pharm 2013
Parvizi J, Gehrke T. International Consensus Meeting on PJI 2013
Meehan J, JBJS Am 2009
Peel TN, AAC 2012
GLYCOPEPTIDE PROPHYLAXIS META-ANALYSIS

- Protective against MRSA SSIs  RR 0.46
- Not protective against MSSA SSIs RR 1.18
- Combination with another agent protective against Gram(+) SSIs  RR 0.22

Schweizer M, BMJ 2013
It is suggested that glycopeptides can be used only in:

1. Institutions with a significant prevalence (e.g., >10-25%) of MRSA and MRSE among orthopaedic patients;
2. Facilities with recent MRSA or incisional MRCNS outbreaks;
3. History of MRSA infection;
4. Known MRSA colonization; and
5. History of life-threatening allergy to β-lactam antibiotics.
6. Institutionalized patients (nursing homes, dialysis etc)
7. Recent hospitalization

Daptomycin: should be considered as an alternative for people with known anaphylactic or severe reaction to glycopeptides

Meehan J, JBJS Am 2009

Moriya K, Smith K. Orthopaedics 2005
Matar WY, JBJS Am 2010 Bratzler DW, ASHP Report, Scottish Intercollegiate Guidelines Network 2009
Galvin KL, JBJS Am 2011
Mangram AJ, Infect Control Hosp Epid 1999
Salkind AR, Am Fam Phys 2011

AAOS 2004
Am J Health Syst Pharm 2013
Prokuski L, AAOS 2008
Wiesel B, Esterhai J. Musculoskeletal Infections 2013
Shuman E, Drug Aging 2011
DUAL ANTIBIOTIC PROPHYLAXIS
eg. cephalosporins plus vancomycin or aminoglycosides

- Routine use of dual antibiotics as AP is not recommended
  Parvizi J, Gehrke T. International Consensus Meeting on PJI 2013

- Some encouraging data from cardiothoracic surgery
  Walsh EE, Arch Intern Med 2011  Dhadwal K, Heart 2007

- Conflicting data in orthopaedic surgery

- May lead to adverse events eg acute kidney injury
  Zhu XX, Clin Orthop Rel Res 2015
  Challagundla SR, Nephrol Dial Transplant 2013
DUAL ANTIBIOTIC PROPHYLAXIS
-teicoplanin plus cefuroxime (CT) vs cefuroxime (C)-

PROPHYLAXIS WITH TEICOPLANIN AND CEFUROXIME REDUCES THE RATE OF PROSTHETIC JOINT INFECTION AFTER PRIMARY ARTHROPLASTY

Tornero E, García-Ramiro S, Martínez-Pastor JC, Bori G, Bosch J, Morata L, Sala M, Basora M, Mensa J, Soriano A

- Retrospective study, Barcelona, Spain 2010-2013, N=1897, THA – TKA
- Cefuroxime 1.5 gm vs cefuroxime plus teicoplanin
- Lower PJI rate in CT group (1.26 % vs 3.51 %, p=0.002)
- Adding teicoplanin is associated with a lower risk of infection (HR 0.35, 95CI: 0.17-0.74)

Antimicrob Agents Chemother 17 Nov 2014
INFECTION AFTER SHOULDER ARTHROPLASTY

- Axilla: sebaceous glands, hair follicles
- Pathogen: *S.aureus*, *S.epidermidis*, *Propiobacterium acnes*  
  *Corynobacterium* spp, polymicrobial
- Incidence: primary TJA 0->2 %, revision TJA up to 16 %
- Chemoprophylaxis: No separate guidelines – Data limited

Saltzmann MD, JAAOS 2011  
Beekman BDA, JBJS Br 2010  
Coste JJ, JBJS Br 2004
ANTIBIOTIC PROPHYLAXIS IN SPECIAL CIRCUMSTANCES

• Routine AP is recommended in patients:
  - undergoing major reconstruction using megaprostheses
  - undergoing reconstruction by bulk allografts
  - with severe diseases (eg. poorly controlled diabetes, immunosuppression etc)

• Antibiotic-impregnated allografts may be useful (especially in the 2nd stage of 2-stage revision)

Parvizi J, Gehrke T. International Consensus Meeting on PJI 2013
INAPPROPRIATE USE OF ANTIBIOTICS

- Surveillance studies indicate that AP is not always administered in a manner supported by scientific evidence
- Predisposes to post-operative infections
- Contributes to antibiotic resistance
- Increases the risk of adverse reactions
- Increases healthcare cost

AAOS 2004, Inf stat 1027
USE OF PERIOPERATIVE ANTIBIOTIC PROPHYLAXIS IN SELECTED SURGICAL PROCEDURES - RESULTS OF A SURVEY IN 889 SURGICAL DEPARTMENT IN GERMAN HOSPITALS

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>Choice of antibiotic</th>
<th>Duration of Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary artery bypass</td>
<td>96%</td>
<td>0%</td>
</tr>
<tr>
<td>Gastric surgery</td>
<td>33%</td>
<td>55%</td>
</tr>
<tr>
<td>Colorectal surgery</td>
<td>30%</td>
<td>43%</td>
</tr>
<tr>
<td>Biliary surgery</td>
<td>38%</td>
<td>51%</td>
</tr>
<tr>
<td>Total hip replacement</td>
<td><strong>81%</strong></td>
<td><strong>41%</strong></td>
</tr>
<tr>
<td>Heart valve replacement</td>
<td>91%</td>
<td>0%</td>
</tr>
<tr>
<td>Overall</td>
<td>49%</td>
<td>43%</td>
</tr>
</tbody>
</table>

### Appropriateness of Antimicrobial Prophylaxis According to Surgical Specialty in Eastern France

<table>
<thead>
<tr>
<th></th>
<th>Orthopaedic surgery N(%)</th>
<th>Digestive surgery N(%)</th>
<th>Urologic surgery N(%)</th>
<th>Vasculat surgery N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proper indication</td>
<td>84.0</td>
<td>92.6</td>
<td>75.3</td>
<td>78.9</td>
</tr>
<tr>
<td>Proper agent</td>
<td>60.6</td>
<td>40.0</td>
<td>11.6</td>
<td>95.0</td>
</tr>
<tr>
<td>Proper duration</td>
<td>70.9</td>
<td>67.2</td>
<td>74.4</td>
<td>65.0</td>
</tr>
</tbody>
</table>

Efficacy of teicoplanin for the prevention of surgical site infections after total hip or knee arthroplasty: a prospective, open-label study

Kyriaki Kanellakopoulou a,c, Antonios Papadopoulos a, Dimitrios Varvaroussis b, Amyntas Varvaroussis b, Evangelos I. Giamarellos-Bourboulis a, Athanassios Pagonas c, Anestis Stergiou b, Panagiotis Papadeli b, Vassilios Nikolaidis d, Helen Giamarello a
Prevalence of methicillin-resistant Staphylococci in KAT Hospital (Greece) during 2003-2004

Varvaroussis D, Thesis, Athens 2010
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Teicoplanin arm</th>
<th>Comparator arm</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>278</td>
<td>338</td>
<td>0.334</td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>70/208</td>
<td>73/265</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± S.D.) (years)</td>
<td>67.40 ± 10.74</td>
<td>70.69 ± 8.01</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Underlying disorders [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM2</td>
<td>33 (11.9)</td>
<td>40 (12.1)</td>
<td>1.000</td>
</tr>
<tr>
<td>COPD</td>
<td>14 (5.0)</td>
<td>25 (7.4)</td>
<td>0.047</td>
</tr>
<tr>
<td>CHD</td>
<td>47 (16.9)</td>
<td>51 (15.1)</td>
<td>0.581</td>
</tr>
<tr>
<td>RA</td>
<td>16 (3.6)</td>
<td>8 (2.4)</td>
<td>0.472</td>
</tr>
<tr>
<td>Type of operation [n (%)]</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>THA</td>
<td>161 (57.9)</td>
<td>104 (30.8)</td>
<td></td>
</tr>
<tr>
<td>TKA</td>
<td>177 (42.1)</td>
<td>234 (69.2)</td>
<td></td>
</tr>
<tr>
<td>Operating time (mean ± S.D.) (h)</td>
<td>2.0 ± 0.9</td>
<td>2.0 ± 1.1</td>
<td>0.45</td>
</tr>
<tr>
<td>Type of comparator [n (%)]</td>
<td></td>
<td>2GC, 163 (48.2%); (-lactam/(-lactamase inhibitor: 153 (45.3), ciprofloxacin, 22 (6.5)</td>
<td></td>
</tr>
<tr>
<td>SSIs</td>
<td>Total Infections</td>
<td>Superficial Infections</td>
<td>Deep Infections</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>------------------</td>
<td>------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td></td>
<td>13 pts (2.29%)</td>
<td>9 (1.55%)</td>
<td>4 (0.7%)</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 pts (0.77%)</td>
<td>0</td>
<td>2 (0.77%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Pseudomonas aeruginosa</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 MS-CNS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Staph. epidermidis)</td>
<td></td>
</tr>
<tr>
<td>Comparator group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11 pts (3.54%)</td>
<td>9 (2.99%)</td>
<td>2 (0.64%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 MRSA</td>
<td>1 MRSA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6 negative cultures</td>
<td>1 MR-CNS</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Staph. hominis)</td>
<td></td>
</tr>
</tbody>
</table>

Results revealed that single-dose teicoplanin was more effective as prophylaxis for total hip or knee arthroplasty compared with multiple doses of broad-spectrum antimicrobials. These results are very
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

Bratzler DW, ASHP Report, Am J Health Syst Pharm 2013
Parvizi J, Gehrke T. International Consensus Meeting on PJI 2013
McHugh JM, JAC 2011 Matar WY, JBJS Am 2010
Scottish Intercollegiate Guidelines Network 2009 ASHP 2010
Jiranek WA, JBJS 2006 Roberts DW, JBJS Am 2013
Prevention of deep infection in joint replacement surgery

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)

Wang J. PLoS ONE 2013

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?

• Small RCTs with conflicting results
• FDA: approval of premixed Ab bone cement (genta, tobra) as AP in 2nd 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
McHugh JM, JAC 2011 Matar WY, JBJS Am 2010
Scottish Intercollegiate Guidelines Network 2009 ASHP 2010
Jiranek WA, JBJS 2006 Roberts DW, JBJS Am 2013
ANTIBIOTIC PROPHYLAXIS (AP) GUIDELINES FOR DENTAL PROCEDURES
AMERICAN DENTAL ASSOCIATION (ADA) / AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS (AAOS) 1997 / 2003 ADVISORY STATEMENT

• **Considered for AP:** - pts within 2 years of TJR and/or
  - pts with immunosuppression or comorbitity (eg. DM, RA)
  AND
  - a dental procedure with a higher incidence of bacteremia

• **AP not indicated:** - pts with pins, plates or screws
  - pts with minor dental procedures

States that: no scientific evidence support AP prior to dental procedures
the risk/benefit and cost/effectiveness ratio do not justify routine AP

• **AAOS 2009:** recommend AP prior any invasive procedure
• **This is not supported by current evidence**
• **INTERNATIONAL CONSENSUS 2013:** Do not recommend routine AP

Parvizi J, Gehrke T. International Consensus Meeting on PJI 2013

JADA 2003
aaos.org
ANTIBIOTICS PROPHYLAXIS PRIOR TO DENTAL PROCEDURES
once 1-2 hours prior to procedure

- Amoxycillin 2 gr
- Azithromycin 500 mg
- Erythromycin 1,5 gr
- Cefaclor 1 gr
- Clindamycin 600 mg
- Moxifloxacin 400 mg

Parvizi J, Gehrke T. International Consensus Meeting on PJI 2013
Chen A, J Orthop Res 2014
PREVENTION OF HAEMATOGEOUS INFECTIONS

- The efficiency of AP after dental procedures has not been convincingly proven

- The rare occurrence (0.05%) of late PJIs should not justify AP on a regular routine basis for standard dental treatments

- Perhaps it is prudent to follow previous recommendations, concerning special high risk groups of patients undergoing invasive dental procedures

- An optimal dental hygiene is of extreme importance in preventing these PJIs

Colterjohn T, J Arthroplasty 2014
Berbari EF, CID 2010
Husted H, Acta Orthopaedica 2014
Berbari E, Baddour L, UpToDate 2014
ADA, AAOS Dental Guidelines 2012. aaos.org
PREVENTION OF HAEMATOGENOUS INFECTIONS

• AP is also indicated in high risk patients after certain urological procedures eg. in increased risk of bacteremia such as after lithotripsy or in surgery involving bowel

• Ciprofloxacin 500 mg pos / 400 mg iv

• Data do not generally support the use of AP after GI endoscopy

• Individualization and consultation with orthopaedic surgeons/ infectious disease specialist is helpful

Parvizi J, Gehrke T. International Consensus Meeting on PJI 2013
THANK YOU
GENERAL PRINCIPLES OF PJI PREVENTION

• Careful pre-operative evaluation for occult infection

• Taper or discontinue immunosuppressive drugs, if possible

• Any local (eg wound) or systemic infection eg UTIs should be quickly eradicated

• Prevention of haematogenous infections

Bratzler DW, CID 2004
Treat Guidel Med Letter 2006
CHRONIC INFECTIONS OF BONE AND ORTHOPAEDIC IMPLANTS: 16 YEAR EXPERIENCE
Giannitsioti E,.. Papadopoulos A et al
Panhellenic Conference of Infection 2008

Culture results

Aποτελέσματα καλλιεργειών στη θετική λοίμωξη
(n=177)

- No pathogen
- others
- M.tuberculosis
- Brucella spp
- Fungi
- Enterococci
- Klebsiella spp
- E.cloacae
- P.aeruginosa
- CoNS
- S aureus
ANTIMICROBIAL PROPHYLAXIS IN SURGERY: A SERIOUS STATEMENT

Third-generation cephalosporins, such as cefotaxime, ceftriaxone, cefoperazone, ceftazidime or ceftizoxime and fourth-generation cephalosporins such as cefepime should **not be used** for surgical prophylaxis because:

- They are expensive.
- Some are less active than cefazolin against staphylococci.
- Their spectrum of activity includes organisms rarely encountered in elective surgery.
- **Their widespread use for prophylaxis promotes emergence of resistance to these valuable drugs.**

*The Medical Letter. 41:75, 1999.*
SECOND STAGE PROCEDURE (REVISION ARTHROPLASTY)

- Risk of recurrent infection due to either:
  - incomplete eradication of prior bacteria
  - new infection

- Coverage of: - prior bacteria
  - most common pathogens in the institution

- Use of antibiotic-laden bone cement

Bratzler DW, ASHP Report, Am J Health Syst Pharm 2013
Parvizi J, Gehrke T. International Consensus Meeting on PJI 2013