Compendium of strategies to prevent healthcare-associated infections
EUCIC, ESGNI

Ways to improve antibiotic surgical prophylaxis

Nicola Petrosillo

National Institute for Infectious Diseases "Lazzaro Spallanzani", IRCCS
Rome, Italy
Conflict Of Interests

Dr. Petrosillo has received lecture fees from MSD, Pfizer, Novartis, Astellas, Angelini, Zambon; and consulting fees for Advisory Boards from MSD, Pfizer, 3M, The Medicines Company, Achaogen, Astellas.
Question

- Male, 73 years old, since 3 years in a nursing home for mental deterioration.
- Weight 100 Kg  BMI 50.
- A previous hospital stay 3 months before.
- Documented allergy to B-lactams
- He should undergo an open biliary tract intervention. His intervention lasts 3 hours.

Antibiotic surgical prophylaxis:
- a. indication: Y  N
- b. If Y, choice of antibiotic______________________________
- c. Dose____________________________________________
- d. Timing____________________________________________
- e. Redosing________________________________________
- f. Duration of prophylaxis______________________________
Main points of antimicrobial surgical prophylaxis

Pre-operative antimicrobial administration

- Selection of intervention (clean+prosthesis/implant, clean contaminated, dirty) (NO! Routinely clean uncomplicated non prosthesis/implant)

- The optimal time for administration is within 60 minutes before surgical incision (better than the previous «at induction of anesthesia»)

- For fluoroquinolones and vancomycin the administration should begin within 120 minutes before surgical incision

Selection and dosing

- Recommendations for selection for specific operations are provided
- Alternative agents are also provided (i.e. allergy to beta-lactams)
- Redosing is needed if the duration of the procedure exceeds 2 half-lives of the drug or there is excessive bleeding during the intervention

Duration of prophylaxis

- Single dose
- Continuation for less than 24 hrs in selected cases
Goals of antimicrobial surgical prophylaxis

1. Use antimicrobials for all operations in which there is evidence that their use in prophylaxis can reduce SSI rates

2. Use an antimicrobial that is safe, inexpensive, and bactericidal, and with a spectrum covering the most probable intra-operative contaminants

3. Warrant a bactericidal concentration of the antimicrobial in serum and tissue by the time of incision

4. Maintain therapeutic levels of the antimicrobial in both serum and tissue throughout the operation and for few hours after its closure in the operating room.
Recommended agents, doses and redosing intervals

- **Cefazolin 2 g (3 g for pts weighing \( \geq 120 \) Kg)** is the main recommended agent

- Redosing at 4 h from initiation of preoperative dose

- **Alternative agents in Pts with B-lactam allergy:** Clindamycin, Vancomycin

- **Clindamycin 900 mg, redosing at 6 hrs**
Antibiotic prophylaxis for surgical site infection in people undergoing liver transplantation (Review)

Heart transplant:
Cefazolin

Lung-Heart transplant:
Cefazolin

Liver transplant:
Piperacillin-tazobactam, cefotaxime+ampicillin

Pancreas and pancreas-kidney transplant:
Cefazolin (+ fluconazole in those with enteric drainage of the pancreas

Bratzler DW et al.
Am J Health-Syst Pharm 2013
Goals of antimicrobial surgical prophylaxis

1. Use antimicrobials for all operations in which there is evidence that their use in prophylaxis can reduce SSI rates

2. Use an antimicrobial that is safe, inexpensive, and bactericidal, and with a spectrum covering the most probable intraoperative contaminants

3. Warrant a bactericidal concentration of the antimicrobial in serum and tissue by the time of incision

4. Maintain therapeutic levels of the antimicrobial in both serum and tissue throughout the operation and for few hours after its closure in the operating room.
When Vancomycin?
Vancomycin in prophylaxis

- Vancomycin prophylaxis should be considered for patients with known MRSA colonization or at high risk for MRSA colonization in the absence of surveillance data (e.g., patients with recent hospitalization, nursing home resident, hemodialysis patients).

- Vancomycin may be included in the regimen of choice when a cluster of MRSA cases (e.g., mediastinitis after thoracic surgery) and MR CNS SSIs have been detected at an institution.

- Data suggest that vancomycin is less effective than cefazolin against MSSA, so vancomycin is used in combination with cefazolin at some institutions with both MSSA and MRSA SSIs.
For infection prophylaxis in surgical patients, current recommendations are that glycopeptides should be limited to those with known MRSA infection or colonisation to limit selection for new glycopeptide-resistant strains. Some sources recommend the use of vancomycin prophylaxis in institutions where the prevalence of MRSA and MRSE is high. This suggests that the benefits of reducing the environmental pressure that promotes the development of vancomycin resistance and reducing the risk of superinfections outweigh the risks [12].

What is a «high» MRSA prevalence?

• Coronary artery by-pass$\rightarrow$ MRSA threshold 3% of infections (Miller LG et al ICHE 2011; Zanetti G et al. EID 2001)

• Vascular surgery$\rightarrow$ a MRSA prevalence of 50% is suggested before a B-lactam is replaced with vancomycin – when reaches 10% add an aminoglycoside (as in guidelines of British Society of Antimicrobial Chemotherapy) (Muralidhar B et al. Eur J Endovasc Surg 2006)
An economic model for the prevention of MRSA infections after surgery: non-glycopeptide or glycopeptide antibiotic prophylaxis?

Aim: to explore whether there is a threshold of MRSA prevalence at which switching to routine glycopeptide-based antibiotic prophylaxis becomes cost-effective

Parameters for use in the model

The parameters in the model were divided into the following categories:

- Baseline infection rates for prophylaxis with a cephalosporin: MRSA and non-MRSA SSI rates.
- Effectiveness estimates for interventions (vancomycin, cephalosporin plus vancomycin) in terms of the relative reduction in superficial and deep/joint infection rates.
- Consequences of superficial and deep/joint infection: impact on survival, length of hospital stay, HRQoL (QALYs) and management of infections.

The model suggests that, where the MRSA infection rate is \( \geq 25\% \) and the rate of other infections with cephalosporin prophylaxis is \( \geq 20\% \), the combination of cephalosporin plus vancomycin is the optimal antibiotic prophylaxis for hip arthroplasty patients.
Goals of antimicrobial surgical prophylaxis

1. Use antimicrobials for all operations in which there is evidence that their use in prophylaxis can reduce SSI rates

2. Use an antimicrobial that is safe, inexpensive, and bactericidal, and with a spectrum covering the most probable intra-operative contaminants

3. Warrant a bactericidal concentration of the antimicrobial in serum and tissue by the time of incision

4. Maintain therapeutic levels of the antimicrobial in both serum and tissue throughout the operation and for few hours after its closure in the operating room.
Duration: always one shot, one day?

• Continuation of antibiotics after surgical incision closure is unnecessary

• In addition there is concern of resistance emergence and C difficile infection.

• 838 patients (elective coronary artery bypass grafting, valve operations) were randomized to a single dose of cefazolin versus 24-h administration.

• Patients receiving single dose prophylaxis suffered an 8.3% rate of SSI, whereas patients a full 24h of post-operative coverage only developed SSI in 3.6% of the cases

Antibiotic prophylaxis in cardiac surgery: systematic review and meta-analysis

Duration: always one shot, one day?

Shorter duration prophylaxis was associated with a higher rate of deep sternal wound infections (OR=1.83) - the difference originated from studies in which the short-duration arm was \(\leq 24\) h post operation.

No difference when the short-duration arm was 48 h
Improving the pharmacokinetics

- This point becomes even more important with the growing epidemic of obesity.

- When determining an appropriate dose of peri-operative antibiotic for individuals weighing more than 30% over their ideal body weight, it is useful to calculate a more appropriate dosing weight.

- The dosing weight can be calculated as

  \[ \text{ideal body weight} + [0.4 \times (\text{total body weight} - \text{ideal body weight})] \]
Improving the pharmacokinetics

• Since 1989 it is known that in obese patients undergoing gastric surgery, serum and tissue levels of cefazolin were consistently below the MIC for pathogens causing SSI in patients who received one-gram vs two-gram prophylaxis (Forse RA et al. Surgery 1989; 106: 750-6)
Perioperative antibiotic prophylaxis in the gastric bypass patient: Do we achieve therapeutic levels?

Table 1. Patient demographics of body mass index (BMI) groups

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>17</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>BMI</td>
<td>47 (±1.3)</td>
<td>53.9 (±2.8)</td>
<td>69.2 (±10.2)</td>
</tr>
<tr>
<td>Males</td>
<td>4</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Female</td>
<td>13</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Age (y)</td>
<td>45.8 (±3.5)</td>
<td>42.4 (±3.2)</td>
<td>40.5 (±3.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>128.5 (±14.5)</td>
<td>145.7 (±19.1)</td>
<td>191.0 (±50.0)</td>
</tr>
<tr>
<td>Laparoscopic</td>
<td>17/17</td>
<td>9/11</td>
<td>7/10</td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>207 (±34.8)</td>
<td>230.9 (±43.5)</td>
<td>235.9 (±44.2)</td>
</tr>
<tr>
<td>Blood loss (cc)</td>
<td>142.2 (±116.4)</td>
<td>202.7 (±234.1)</td>
<td>160 (±191.6)</td>
</tr>
<tr>
<td>Fluid administration (mL)</td>
<td>3,571 (±376)</td>
<td>3,250 (±500)</td>
<td>5,000 (±767)</td>
</tr>
<tr>
<td>Fluid mL/kg</td>
<td>28.3 (±5.8)</td>
<td>24.9 (±4.9)</td>
<td>19.7 (±2.9)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3/17</td>
<td>1/11</td>
<td>2/10</td>
</tr>
<tr>
<td>Surgical site infection</td>
<td>3/17</td>
<td>1/11</td>
<td>3/10</td>
</tr>
</tbody>
</table>

2g 1h before incision, and 2 g after 3 h
<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Standard dose</th>
<th>Weight-based dose recommendation</th>
<th>Recommended redosing interval, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>1–2 g iv</td>
<td>20–30 mg/kg (if &lt;80 kg, use 1 g; if &gt;80 kg, use 2 g)</td>
<td>2–5</td>
</tr>
<tr>
<td>Cefoxitin</td>
<td>1–2 g iv</td>
<td>20–40 mg/kg</td>
<td>2–3</td>
</tr>
<tr>
<td>Cefotetan</td>
<td>1–2 g iv</td>
<td>20–40 mg/kg</td>
<td>3–6</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>400 mg iv</td>
<td>400 mg</td>
<td>4–10</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>900 mg iv</td>
<td>If &lt;10 kg, use at least 37.5 mg; if &gt;10 kg, use 3–6 mg/kg</td>
<td>3–6</td>
</tr>
<tr>
<td>Erythromycin base</td>
<td>1 g po 19, 18, and 9 h before surgery</td>
<td>9–13 mg/kg</td>
<td>NA</td>
</tr>
<tr>
<td>Neomycin</td>
<td>1 g po 19, 18, and 9 h before surgery</td>
<td>20 mg/kg</td>
<td>NA</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>0.5–1 g iv</td>
<td>15 mg/kg initial dose (adult); 7.5 mg/kg on subsequent doses</td>
<td>6–8</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1 g iv</td>
<td>10–15 mg/kg (adult)</td>
<td>6–12</td>
</tr>
</tbody>
</table>

*aAdapted from Bratzler and Houck [80].
*bDose may vary with renal function.
*cData are primarily from published pediatric recommendations.
*dFor procedures of long duration, antimicrobial agents should be redosed at intervals of one to two times the half-life of the drug. The intervals in the table were calculated for patients with normal renal function.
Vancomycin for Surgical Prophylaxis?

Tonya Crawford,1 Keith A. Rodvold,1 and Joseph S. Solomkin2

Figure 1. Serum vancomycin concentrations during cardiopulmonary bypass surgery. A, Administration of vancomycin (1-hour infusion). B, C, Hemodilution with cardioplegic solution. C, D, Clamping of the aorta and induction of hypothermia causes a decrease in the serum vancomycin concentration. D, E, Rewarming process causes an increase in the vancomycin concentration as the serum and tissue concentrations are reaching equilibrium. E, F, Elimination of vancomycin from the serum is resumed once the patient’s condition is hemodynamically stable.
Pharmacokinetic–pharmacodynamic aspects of antimicrobial prophylaxis with teicoplanin in patients undergoing major vascular surgery

A prospective, two-arm, open study assessing plasma exposure to teicoplanin with two prophylaxis regimens:

Group A (#23) → 800 mg vs Group B (#24) 400 mg pre + 2 doses of 200 mg 24 h apart

therapeutically effective plasma concentrations (>10 mg/L) of teicoplanin
They assessed SAP appropriateness in a regional prospective multicenter study on the basis of the agreement of the Surgical Care Improvement Project indicators (SCIP-Inf) with Italian guidelines (GL).

Prophylaxis was administered in 2,664 of 2,835 procedures (94%): In 2,346 of 2,468 (95%) as indicated and in 318 of 367 (86.6%) in which they were not indicated.

The SCIP-Inf1 (timing), SCIP-Inf2 (antibiotic choice), and SCIP-Inf3 (duration) were in agreement with GL in 1,172 (50%), 1,983 (84.5%), and 1,121 (48%) of 2,346 procedures, respectively.
Retrospective audit→ adherence was poor (less than 20%). Most frequent error was drug choice. Errors in timing were frequent, with prophylaxis typically occurring excessively early.

Logistic regression identified emergency surgery as independent factor with prophylactic errors.

### Table 3. Sub-Categorization of Adherence Error Types

<table>
<thead>
<tr>
<th></th>
<th>Blacktown Hospital n=167</th>
<th>Lismore Base Hospital n=161</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug choice</td>
<td>119 (71.3)</td>
<td>112 (69.6)</td>
</tr>
<tr>
<td>Dose</td>
<td>2 (1.2)</td>
<td>16 (9.9)</td>
</tr>
<tr>
<td>Insufficient</td>
<td>0</td>
<td>5 (3.1)</td>
</tr>
<tr>
<td>Excessive</td>
<td>2 (1.2)</td>
<td>11 (6.8)</td>
</tr>
<tr>
<td>Timing</td>
<td>84 (50.3)</td>
<td>80 (50)</td>
</tr>
<tr>
<td>Early (&gt;60 min)</td>
<td>62 (37.1)</td>
<td>52 (32.5)</td>
</tr>
<tr>
<td>Late</td>
<td>22 (13.2)</td>
<td>28 (17.5)</td>
</tr>
<tr>
<td>Duration</td>
<td>20 (12)</td>
<td>48 (29.8)</td>
</tr>
<tr>
<td>Redosing</td>
<td>13 (7.8)</td>
<td>15 (9.3)</td>
</tr>
<tr>
<td>Not performed</td>
<td>13 (7.8)</td>
<td>13 (8.1)</td>
</tr>
<tr>
<td>Performed, but inappropriately</td>
<td>0</td>
<td>2 (1.2)</td>
</tr>
</tbody>
</table>

Consideration should be given to multidisciplinary involvement of anesthetists, implementation of focused interventions with an emphasis on emergency settings.
Educational Antimicrobial Stewardship Intervention Ineffective in Changing Surgical Prophylactic Antibiotic Prescribing

Clinic focused educational ASP, 2014, Australia. Before-after analysis on 100:100 abdominal interventions

### Table 2. Sub-categorization of Adherence Error Types

<table>
<thead>
<tr>
<th>Multi-faceted Intervention</th>
<th>Pre-intervention (n=100)</th>
<th>Post-intervention (n=100)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Computer-based antibiotic prescribing system also for surgical prophylaxis.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Display of prophylactic guidelines in the operating suite; included major surgical procedures, drug choices, dosages, duration, allergy, timing for standard and vancomycin.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Error</td>
<td>18</td>
<td>15</td>
<td>p = 0.568</td>
</tr>
<tr>
<td>Error</td>
<td>82</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>Inappropriately withheld</td>
<td>5 (6.1)</td>
<td>3 (3.5)</td>
<td>p = 0.721</td>
</tr>
<tr>
<td>Drug Choice</td>
<td>59 (72)</td>
<td>60 (70.6)</td>
<td>p = 0.955</td>
</tr>
<tr>
<td>Dosage</td>
<td>1 (1.2)</td>
<td>1 (1.2)</td>
<td>p = 1.000</td>
</tr>
<tr>
<td>Timing</td>
<td>40 (48.8)</td>
<td>44 (51.8)</td>
<td>p = 0.604</td>
</tr>
<tr>
<td>Duration</td>
<td>8 (9.8)</td>
<td>12 (14.1)</td>
<td>p = 0.357</td>
</tr>
<tr>
<td>Re-dosing</td>
<td>4 (4.9)</td>
<td>9 (10.6)</td>
<td>p = 0.156</td>
</tr>
</tbody>
</table>
Compliance: how can we improve it?

Adherence to surgical antibiotic prophylaxis remains a challenge despite multifaceted interventions

Intervention Cycle #1
1. Pre-incisional checklist modification with antibiotic checkpoints
2. Computerized physician order entry (CPOE) order set for preoperative antibiotics

Intervention Cycle #2
1. Anesthesia team assigned role of antibiotic administration
2. Antibiotic guidelines attached to all anesthesia carts in operating rooms

Guideline Modification
Due to increased SSIs from MRSA in head and neck operations

Putnam LR et al. Surgery 2015; 158:413-9
Adherence to surgical antibiotic prophylaxis remains a challenge despite multifaceted interventions

Table III. Adherence to antibiotic guidelines, 2011–2014

<table>
<thead>
<tr>
<th>Component</th>
<th>2011 (n = 93)</th>
<th>2012 (n = 185)</th>
<th>2013 (n = 192)</th>
<th>2014 (n = 159)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Correct type</td>
<td>98%</td>
<td>94%</td>
<td>96%</td>
<td>70%</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Correct dose</td>
<td>81%</td>
<td>75%</td>
<td>63%</td>
<td>84%</td>
<td>.57</td>
</tr>
<tr>
<td>Correct timing</td>
<td>80%</td>
<td>82%</td>
<td>83%</td>
<td>89%</td>
<td>.10</td>
</tr>
<tr>
<td>Correct redosing</td>
<td>7%</td>
<td>21%</td>
<td>17%</td>
<td>53%</td>
<td>.02</td>
</tr>
<tr>
<td>Overall adherence</td>
<td>55%</td>
<td>55%</td>
<td>49%</td>
<td>55%</td>
<td>.38</td>
</tr>
</tbody>
</table>

- CPOE has been demonstrated in a systematic review (van Rosse F et al. Pediatrics 2009; 123:1184-90) to reduce medication prescription errors.
- In their study CPOE was poor with use in less than 2% of all operations

Putnam LR et al. Surgery 2015; 158:413-9
Description of a multidisciplinary initiative to improve SCIP measures related to pre-operative antibiotic prophylaxis compliance: a single-center success story

Table 2 Provider non-compliance episodes by quarter

<table>
<thead>
<tr>
<th>Department</th>
<th>2010 N (%)</th>
<th>2011 N (%)</th>
<th>2012 N (%)</th>
<th>2013 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q2</td>
<td>Q3</td>
<td>Q4</td>
<td>Q1</td>
</tr>
<tr>
<td>Anesthesiology</td>
<td>6</td>
<td>10</td>
<td>27</td>
<td>7</td>
</tr>
<tr>
<td>Surgery</td>
<td>12</td>
<td>8</td>
<td>33</td>
<td>19</td>
</tr>
<tr>
<td>All</td>
<td>17</td>
<td>18</td>
<td>60</td>
<td>26</td>
</tr>
</tbody>
</table>

Figure 1 Provider Notification Letters by Quarter and Department.

Sutherland et al. Patient Safety in Surgery 2014, 8:37
# Systematic review and evidence-based guidance on perioperative antibiotic prophylaxis

## Perioperative antibiotic prophylaxis modality

### Modality #1: Multidisciplinary antimicrobial management teams

Hospitals should establish a multidisciplinary AM team (including surgeons, anaesthesiologists, nurses, pharmacists, infection control specialists, and clinical microbiologists) who should develop and implement a protocol of appropriate PAP.

*Compliance with this protocol should be audited regularly and the results should be fed back to the antimicrobial prescribers and decision-makers, e.g. chief of surgery, quality committees AM team.

*The protocol should be reviewed and updated regularly. It should consider adjustment of PAP for patients who are at risk for SSI due to MRDs or who have a BMI over 30. The hospital's local antibiotic susceptibility patterns should also be taken into account.*

### Modality #2: Responsibility for appropriate timing of perioperative antibiotic prophylaxis

To ensure appropriate timing, antibiotic prophylaxis before and during surgery should be the responsibility of the anaesthesiologist*.

*This recommendation is supported by the best available evidence. If there is no anaesthesiologist available, another professional present at the time of surgery should be designated.*

### Modality #3: Timing of perioperative antibiotic prophylaxis

PAP should be administered within 60 minutes before incision (except when administering vancomycin and fluoroquinolones), ideally at the time of anaesthetic induction.

### Modality #4: Dosing and duration of perioperative antibiotic prophylaxis

Although a single dose of PAP is preferred, subsequent doses should be given depending on the duration of the procedure and the half-life of the antibiotic, and if significant blood loss occurs during surgery.

### Modality #5: Duration and termination of perioperative antibiotic prophylaxis

Continuing antibiotic prophylaxis after the end of surgery is not recommended*.

*Hospitals should use a reminder/stop order system (e.g. computer system, checklist) in order to encourage appropriate duration and dosage of PAP.

### Indicators for each modality

- The presence of a multidisciplinary AM team which is responsible for developing, implementing and regularly updating the PAP protocol, in charge of regularly updating the local AB protocol, and responsible for regularly analysing and auditing compliance with appropriate PAP.

- Measurement of the presence of an anaesthesiologist or another designated professional at surgery who is responsible for applying PAP.

- Rate of compliance with the administration of PAP within 60 minutes.

- Rate of compliance with indication, selection and dosage of PAP according to protocol.

- Rate of compliance with discontinuation of PAP within 24 hours after initiation of surgery.
Male, 73 years old, since 3 years in a nursing home for mental deterioration.
Weight 100 Kg  BMI 50.
A previous hospital stay 3 months before.
Documented allergy to B-lactams
He should undergo an open biliary tract intervention. His intervention lasts 3 hours.

Antibiotic surgical prophylaxis:
a. Indication: YES
b. Choice of antibiotic VANCOMYCIN
c. Dose 15 mg/Kg → 1,5 g

d. Timing: 120 minutes before surgical incision (due to prolonged infusion time)
e. Redosing NO
f. Duration of prophylaxis ONE SHOT/ONE DAY