Antibiotic Management of Prosthetic Joint Infections

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Declarations of interest

• Consultancy
  – Novartis
  – Pfizer
  – Astrazeneca
  – Astellas
  – Cubist

• Research funding
  – Novartis
55 year old male, December 2014

• Sepsis + R Hip pain
• Background
  – COPD
  – Depression
  – Recent nasal polypectomy
  – LTHR 2004, RTHR 2009 (complicated)
• Medication
  – Oxycodone, Fluoxetine, Amitriptyline, Diazepam
Orthopaedic History (1)

23/11/09 RTHR

10/12/09 One Stage Rev

Gp G Strep BCs + intra-op

IV Ceftriaxone (OPAT) Then PO Amox 3 months
Orthopaedic History (2)

23/11/09
RTHR

10/12/09
One Stage Rev

19/04/10
1st Stage Rev

21/06/10
2nd Stage Rev

Gp G Strep BCS + intra-op

IV Ceftriaxone (OPAT)
Then PO Amox 3 months

NG

IV Cef + Rif (OPAT)
6 weeks

NG
Orthopaedic History (3)

23/11/09
RTHR

10/12/09
One Stage Rev

19/04/10
1st Stage Rev

21/06/10
2nd Stage Rev

23/07/12
1st Stage Rev

17/09/12
2nd Stage Rev

Gp G Strep BCs + intra-op

IV Ceftriaxone (OPAT)
Then PO Amox 3 months

NG

IV Cef + Rif (OPAT) 6 weeks

CNS 4/7

IV Teicoplanin (OPAT) 6 weeks

CNS 1/7
• GBS (7 samples)
  – **Sensitive**: Penicillin, Vancomycin, Ceftriaxone, Linezolid
  – **Resistant**: Doxycycline, Clindamycin, Levofloxacin

• Antibiotic Rx?
Antibiotic considerations

- Activity vs organism
- Penetration to site of infection
- (Activity in biofilm)
- Drug-Drug-Host interactions
- Side effects
- IV or oral
- Length of Rx
- Synergy
• GBS (7 samples)
  – **Sensitive:** Penicillin, Vancomycin, Ceftriaxone, Linezolid
  – **Resistant:** Doxycycline, Clindamycin, Levofloxacin

• Antibiotic Rx?

**Oxycodone**
**Fluoxetine**
**Amitriptyline**
**Diazepam**
8 Interactions Found

Contraindicated

Linezolid + Fluoxetine
Linezolid and Fluoxetine both increase serotonin levels. Never use combination. Linezolid may increase serotonin as a result of MAO-A inhibition. If linezolid must be administered, discontinue serotonergic drug immediately and monitor for CNS toxicity. Serotonergic therapy may be resumed 24 hours after last linezolid dose or after 5 weeks of monitoring, whichever comes first.

Serious – Use Alternative

Linezolid + Amitriptyline
Linezolid and Amitriptyline both increase serotonin levels. High likelihood serious or life-threatening interaction. Contraindicated unless benefits outweigh risks and no alternatives available. Linezolid may increase serotonin as a result of MAO-A inhibition. If linezolid must be administered, discontinue serotonergic drug immediately and monitor for CNS toxicity. Serotonergic therapy may be resumed 24 hours after last linezolid dose or after 2 weeks of monitoring, whichever comes first.

Serious – Use Alternative

Linezolid + Oxycodone
Linezolid increases toxicity of Oxycodone by unknown mechanism. Possible serious or life-threatening interaction. Monitor closely. Use alternatives if available. Risk of hypotension, hyperpyrexia, somnolence, or death; separate by 14 d.
Before Treatment: Prevention

- Patient factors: age, obesity, co-morbidity (DM)
- Asepsis, theatre airflow, maintain “normothermia”
- MSSA decolonisation
- Antibiotic prophylaxis: up to 24 hours (Norwegian arthroplasty study)
  - UK favours single dose
  - Choice: Fluclox + Gent associated with increase in risk of AKI (reversible), Cefuroxime: CDI risk
- Antibiotic-impregnated cement: Gent, Clinda, Vanc
- Negative pressure: “Jubilee dressing”
- Hand hygiene, ward environment, Pt education
Cox regression-adjusted survival curves of THRs performed in Norway from 1987 to 1995. The probabilities of survival were calculated with revisions due to infection as the endpoint for patients receiving different antibiotic regimes for prophylaxis. The p value refers to a test of homogeneity showing a statistically significant difference in survival among the regimes.
Accepted wisdom?

“Osteomyelitis is rarely controlled without the combination of careful, complete surgical debridement and prolonged parenteral antibiotic therapy at high dosage”

Waldvogel et al
Surgical approach

• Debridement of bone, Removal of polyethylene and metal work
• Antibiotic-impregnated spacers: Gentamicin, Vancomycin
• Retention of metal work only if
  – Acute infection
  – very recent implant i.e. before formation of biofilm
  – Inoperable
Aim of Surgery: cure or suppress infection and maintain function

Prosthetic Joint Infection

2 Stage Revision
- If >30 days post implant or >3 weeks of symptoms
  - CURE

I Stage Revision
- If <30 days post implant or < 3 weeks of symptoms
  - Debridement and Retention
    - If <30 days post implant or < 3 weeks of symptoms
      - OR Revision not possible
        - CURE or SUPRESS
    - Excision arthroplasty
      - Bone stock, AMR, (Multiple) failed revisions
        - Specialist orthopaedic decision
        - CURE
  - Amputation

Osman et al CID 2013; 56: 1
Aim of antibiotic therapy

• To deliver an optimum concentration of antibiotic to which the organism is sensitive, direct to the site of infection to effect a cure
• To augment/support (but not replace) the surgical approach
• For agents with time dependent characteristics, concentration must remain above the MIC of the organism for the maximum duration of the dosing interval
Route of administration in PJI

- Topical: Beads/ cement (primary or adjunct Rx)
- Intra-articular: infusion
- Oral
- Intravenous (+/- Oral, +/- Topical)
- Intramuscular
Factors affecting antibiotic bone penetration

- Reduced penetration if:
  - Low concentration of drug at site of infection
  - Cortical bone (c.f. cancellous)
  - Poor vascularity
  - Uninfected/uninflammed
  - Presence of biofilm
Free drug concentration correlates with concentration in bone (in $\beta$-lactams)

Scaglioni et al AAC 1997; 41: 2292
PK / PD Principles

C<sub>max</sub> → IV delivered β-lactam

PK/PD parameters

- C<sub>max</sub>/MIC
- AUC/MIC
- T>MIC

Concentration (mg/L)

TIME (h)

T>MIC
PK / PD Principles

IV delivered $\beta$-lactam

PO delivered $\beta$-lactam

PK/PD parameters

$C_{\text{max}}$/MIC
AUC/MIC
T>MIC

$C_{\text{max}}$

Concentration (mg/L)

TIME (h)

T>MIC

MIC
PK / PD Principles

IV delivered β-lactam

PO delivered β-lactam

“Free concentration”

PK/PD parameters

C_{max}/MIC
AUC/MIC
T>MIC

T>MIC
TIME (h)

Concentration (mg/L)

C_{max}
PK / PD Principles

PO delivered β-lactam

PO delivered β-lactam “Free concentration”
β-lactams and bone penetration

β-lactams penetrate bone at approximately 5-20% of serum concentrations (oxacillin, cefazolin, ceftriaxone, ceftazidime, piperacillin, meropenem, aztreonam all studied)

IV delivered [β-lactam] far exceed the MICs of likely organisms in most cases (free concentration is adequate)

Serum concentration of oral delivered β-lactams <10% of IV therefore unlikely to achieve adequate bone concentration

Spellberg, Lipsky CID 2012; 54: 393
β-lactams and bone penetration

Historical data support oral penicillins when used in combination with probenecid

• Reduction in renal excretion
• Higher peak serum concentration
• Limited data available

No licence for this use

Widely used in SSTI in Aus/NZ

SM Bell, Med J Aust 1976; 2: 592
Vancomycin: non infected bone

Graziani et al AAC 1988; 32: 1320

7-13% of serum concentration (- free drug concentration)
Vancomycin: infected bone

Fig. 1. Vancomycin concentrations in plasma and bone versus time.

20-89% of serum concentration (Corticol vs Cancellous)
Teicoplanin: infected bone

12-49% of serum concentration

Fig. 3. Teicoplanin concentrations in plasma and bone versus time.
Daptomycin 8mg/kg Penetration into Bone

Montange et al. Antimicrobial agents and Chemotherapy, 2014; 58: 3991-3996

71.3 [39.4-110.3]
22.4 [13.1-35]
3.1 [1.4-5.7]
Daptomycin in bone (DFI)

Potential advantages of IV therapy

- Mode of delivery for Beta lactams, GPs, Daptomycin
- Acute: sepsis / infection beyond the bone
  - e.g. SAB, Endocarditis, severe SSTI
- Bioavailability
  - Reliable serum concentration following IV administration
  - Avoids problems with absorption
  - Ability to deliver bigger doses
  - Increased likelihood of achieving therapeutic concentration at site of infection
- Spectrum of activity (for certain agents)
- Chronic: compliance and tolerability
  - Missed doses are less likely
Good practice recommendations for outpatient parenteral antimicrobial therapy (OPAT) in adults in the UK: a consensus statement

1. OPAT team and service structure
2. Patient selection
3. Antimicrobial management and drug delivery
4. Monitoring of the patient during OPAT
5. Outcome monitoring and clinical governance
Potential disadvantages of IV therapy

- Requires an IV device
  - Painful to insert
  - Source of infection/ SAB
  - Thrombosis/ phlebitis / fracture
  - Inconvenient dosing regimens
- Requires hospitalisation or OPAT
  - Time consuming to administer
  - Restrictions of device / Hassle
  - Expensive
- Antimicrobial stewardship
  - Use of agents associated with CDI
  - May be unnecessarily broad spectrum
Clinical outcome data

- Mainly observational studies with few RCTs
- Too many variables make comparisons between different IV agents difficult
  - Surgical approach
  - Variable methodology
  - Definitions of success
  - Length/ consistency of follow up
Outcomes in OPAT Rx Osteomyelitis (n=454)

Tice et al JAC 2003; 51: 1261
Outcomes in OPAT Rx OM (n=198)

Kaplan-Meier survival estimate of time to treatment failure for all patients showing all follow-up data available.

Kaplan-Meier survival estimate of time to treatment failure for all patients with OM per diagnosis

19 of 65 with PJI failed (71% success):
Surgery, related or unrelated admission, or unplanned prolongation of IV Rx

Teicoplanin for Bone infection in Glasgow OPAT

• Indications
  – Resistant staphylococcal infections (CoNS or MRSA)
  – Gram-positive infections with β-lactam allergy
  – Prior failure with β-lactams

• Dosing regimen
  – Loading: 20 mg/kg for 3 days (inpatient or outpatient)
  – Maintenance: 3×/week (butterfly)
  – TDM at longest interval (72 hours)
  – Target trough concentration for Bone infection: 20–30 μg/ml
    • <20 μg/ml: increase dose or reduce interval (alt. days)
    • >30 μg/ml: reduce dose or increase interval (2× or 1×/week)

Hazard Ratio from Survival analysis (Cox regression) for the association of the initial IV Antibiotic with failure over the follow up period

<table>
<thead>
<tr>
<th>Initial IV Rx</th>
<th>No.</th>
<th>No. Failing</th>
<th>Hazard ratio</th>
<th>CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teicoplanin</td>
<td>140</td>
<td>48 (34%)</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>51</td>
<td>10 (19.6%)</td>
<td>0.54</td>
<td>0.27-1.06</td>
<td>0.074</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Debridement, Antibiotics and Implant Retention (DAIR)

- 6 weeks IV AB
  - Empiric
    - Vanc + Meropenem
  - Rationalized
    - Ceftriaxone
    - Teicoplanin
- ~12 months oral

Byren et al JAC 2009; 63: 1264
DAIR and duration of IV Rx

Multiple Cox regression model
HR 0.49 (0.18-1.37), p=0.18

Byren et al JAC 2009; 63: 1264
Daptomycin in Bone infection: Observational data to 30 days post-Rx
Daptomycin vs SOC in 2 Stage Revision (Phase II study)

- Microbiological confirmed PJI
- Randomised: 6-8mg/kg Dapto vs GP/SSP
- No oral agent
- 6 weeks post 1\textsuperscript{st} stage
- TOC 2 weeks post 2\textsuperscript{nd} stage
- If success reviewed @3-4 months
- 75 pts randomised

Byren et al ACC 2012; 56: 5626
The MIC for daptomycin remained below the susceptibility breakpoint of ≤1 μg/ml for all staphylococcal isolates in patients with microbiological failure, with no increases in daptomycin MIC for isolates obtained at the first surgery compared with isolates obtained at reimplantation.

Byren et al ACC 2012; 56: 5626
Important Side-effects in OPAT agents

- Ceftriaxone: Rash, LFTs, diarrhoea, leucopenia
- Teicoplanin: Leucopenia, anaemia, TCP, fevers
- Daptomycin: CPK/ myotoxicity, Eosinophilic pneumonitis
Relative frequency of adverse drug reaction (ADR) types, in all first OPAT episodes over 10 year study period.

Note: An ADR in an individual patient in some instances involved multiple drug reaction types (e.g. rash and fever); each ADR type is counted separately in frequency bars even where they stem from one ADR event.
ADRs, Infection Type and AB Used

- Daptomycin
- Ceftriaxone
- Teicoplanin

% with ADR

Infection Types:
- CVS
- BJI
- SSTI
- Bacteraemia
- Daptomycin
- Ceftriaxone
- Teicoplanin
Line related complications in OPAT

- Infection: 0 to 3 per 1000 OPAT patient days
  - Associated with length of IV Rx
- Other line events
  - thrombosis, mechanical and chemical phlebitis: 5 to 50 per 1000 OPAT patient days
  - lowest risk in tunnelled central venous catheters
  - Highest risk when flucloxacillin primary OPAT agent
- No additional risk of patient/ carer administration

Reasons for admission from OPAT

- Deterioration in infection: 76
- Planned surgery: 63
- Adverse drug reaction: 38
- Other planned admission: 28
- Unplanned surgery: 20
- Line complication: 12
- Logistics/transport: 11
- Health care associated infection: 7
- Unrecorded reason: 0
- New medical event, not infection: 0
Comparison of IV s Oral Rx: End of Rx

Review: Antibiotics for treating chronic osteomyelitis in adults
Comparison: 1 Oral antibiotic versus parenteral antibiotic (AB)
Outcome: 1 Remission at the end of treatment

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Oral AB n/N</th>
<th>Parenteral AB n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentry 1990</td>
<td>30/31</td>
<td>27/28</td>
<td></td>
<td>45.7%</td>
<td>1.00 [0.91, 1.10]</td>
</tr>
<tr>
<td>Gentry 1991</td>
<td>18/19</td>
<td>13/14</td>
<td></td>
<td>24.1%</td>
<td>1.02 [0.85, 1.22]</td>
</tr>
<tr>
<td>Gomis 1999</td>
<td>11/16</td>
<td>8/16</td>
<td></td>
<td>12.9%</td>
<td>1.38 [0.76, 2.48]</td>
</tr>
<tr>
<td>Mader 1990</td>
<td>11/14</td>
<td>10/12</td>
<td></td>
<td>17.3%</td>
<td>0.94 [0.65, 1.37]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>80</strong></td>
<td><strong>70</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>1.04 [0.92, 1.18]</strong></td>
</tr>
</tbody>
</table>

Total events: 70 (Oral AB), 58 (Parenteral AB)
Heterogeneity: Chi² = 1.87, df = 3 (P = 0.60); I² = 0.0%
Test for overall effect: Z = 0.70 (P = 0.48)
Test for subgroup differences: Not applicable

Conterno, Turchi, Cochrane review Sep 2013
Comparison of IV vs Oral Rx: ≥ 12 months post Rx

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Oral AB n/N</th>
<th>Parenteral AB n/N</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentry 1990</td>
<td>24/31</td>
<td>22/28</td>
<td></td>
<td>48.5%</td>
<td>0.99 [0.75, 1.29]</td>
</tr>
<tr>
<td>Gentry 1991</td>
<td>14/19</td>
<td>12/14</td>
<td></td>
<td>29.0%</td>
<td>0.86 [0.61, 1.21]</td>
</tr>
<tr>
<td>Mader 1990</td>
<td>11/14</td>
<td>10/12</td>
<td></td>
<td>22.6%</td>
<td>0.94 [0.65, 1.37]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>64</strong></td>
<td><strong>54</strong></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>0.94 [0.78, 1.13]</strong></td>
</tr>
</tbody>
</table>

Total events: 49 (Oral AB), 44 (Parenteral AB)
Heterogeneity: Chi² = 0.38, df = 2 (P = 0.83); I² = 0.0%
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable

Conterno, Turchi, Cochrane review Sep 2013
Quinolones

- Cipro most studies but extrapolate for Levofloxacin
- High oral bioavailability
- Penetrates macrophages and neutrophils
- High bone: serum concentration (>7.3)
- Bone concentration is proportional to dose and in excess of MIC of sensitive organisms.
  - [Bone] 2-10 ug/g
- Effective vs MSSA, CNS, GNB
- In G+ve infection advisable to use 2\textsuperscript{nd} agent to reduce R risk
- Beware QTc prolongation, drug interactions
Rifampicin

- High oral bioavailability
- Penetrates neutrophils
- Excellent bone penetration (1.7ug/g)
- Active in biofilm ++
- Synergistic with other agents
- R develops quickly ++
- Use only in combination (consider delay in administration)
- Drug interactions, LFTs
FIG. 2. Cure rates of infection for antibiotic combinations with rifampin at day 11. Data for antibiotics alone are not shown. LNZ, linezolid; VAN, vancomycin; RIF, rifampin; DAP45, daptomycin at 45 mg/kg/day; DAP100, daptomycin at 100 mg/kg/day.
Other Oral Antibiotics useful in PJI

- Sodium fusidate: caution statins, LFTs
- Trimethoprim: caution CKD, K+
- Doxycycline: chelated by Fe, Ca, ant acids
- Clindamycin: CDI, LFTs
- Linezolid: Haem toxicity, neuropathy. Caution with RIF, other D-DIs
- Pristinamycin (unlicensed)
Table 2. Percentage penetration of linezolid in osteo-articular tissue and fluid for corresponding serum concentration

<table>
<thead>
<tr>
<th></th>
<th>SF (%)</th>
<th>Synovium (%)</th>
<th>Muscle (%)</th>
<th>Bone (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>84.4</td>
<td>48.4</td>
<td>64.5</td>
<td>17.7</td>
</tr>
<tr>
<td>Case 2</td>
<td>133.7</td>
<td>107.9</td>
<td>161.8</td>
<td>97.8</td>
</tr>
<tr>
<td>Case 3</td>
<td>70.1</td>
<td>49.8</td>
<td>65.3</td>
<td>15.5</td>
</tr>
<tr>
<td>Case 4</td>
<td>107.3</td>
<td>98.9</td>
<td>82.1</td>
<td>43.6</td>
</tr>
<tr>
<td>Case 5</td>
<td>93.2</td>
<td>102.8</td>
<td>104</td>
<td>43</td>
</tr>
<tr>
<td>Case 6</td>
<td>125.3</td>
<td>121.1</td>
<td>59.6</td>
<td>47</td>
</tr>
<tr>
<td>Case 7</td>
<td>64.5</td>
<td>62.7</td>
<td>70.5</td>
<td>24.9</td>
</tr>
<tr>
<td>Case 8</td>
<td>88</td>
<td>94.3</td>
<td>100</td>
<td>52.8</td>
</tr>
<tr>
<td>Case 9</td>
<td>85.8</td>
<td>92.7</td>
<td>81.8</td>
<td>37.1</td>
</tr>
<tr>
<td>Case 10</td>
<td>66.4</td>
<td>43</td>
<td>45.1</td>
<td>22</td>
</tr>
<tr>
<td>Mean</td>
<td>91.9</td>
<td>82.2</td>
<td>83.5</td>
<td>40.1</td>
</tr>
<tr>
<td>±S.D.</td>
<td>23.8</td>
<td>28.4</td>
<td>32.9</td>
<td>24.1</td>
</tr>
</tbody>
</table>
### IDSA PJI Guidelines

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Organism</th>
<th>IV Antibiotic</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAIR</td>
<td>Staph</td>
<td>Flucloxacillin, Ceftriaxone, Or Vancomycin, Daptomycin, Linezolid (IV/PO) With Rifampicin</td>
<td>2-6 weeks then oral combination Rx including RIF Total 3 months: THR, other 6 months: TKR</td>
</tr>
<tr>
<td>DAIR</td>
<td>Other</td>
<td>Pathogen specific IV or highly bio available oral combination</td>
<td>4-6 weeks then potentially indefinite suppressive Rx (?avoid RIF)</td>
</tr>
<tr>
<td>Amputation</td>
<td>Any</td>
<td>Pathogen specific IV or highly bio available oral combination</td>
<td>24-48 hrs post amputation unless sepsis 4-6 weeks if residual infection</td>
</tr>
</tbody>
</table>

Osman et al CID 2013; 56: 1
### IDSA PJI Guidelines

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Organism</th>
<th>IV Antibiotic</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>One Stage Revision</td>
<td>Staph</td>
<td>Flucloxacillin Ceftriaxone Or Vancomycin Daptomycin Linezolid (PO) With Rifampicin</td>
<td>2-6 weeks then oral Rx Total 3 months: Rif + other Longer if required</td>
</tr>
<tr>
<td>One Stage Revision</td>
<td>Other</td>
<td>Pathogen specific IV or highly bio available oral combination</td>
<td>4-6 weeks then potentially indefinite suppressive Rx (?avoid RIF)</td>
</tr>
<tr>
<td>Resection arthroplasty / 1\textsuperscript{st} of 2 stage revision</td>
<td>Any</td>
<td>Pathogen specific IV (without Rifampicin) or highly bio available oral combination</td>
<td>4-6 weeks then stop</td>
</tr>
</tbody>
</table>

Osman et al CID 2013; 56: 1
OVIVA study

- Comparing IV vs oral approach in OM (including PJI) 6/52 Rx
- Randomisation within 7 days of surgery or commencement of IV Abx
Conclusions

• Use a best guess/tailored IV antibiotic which will cover the likely/proven organisms
  – Empirical and acute settings
• Use high dose therapy for optimum PK/PD
• Combine with Rifampicin if Staphylococcal infection and the aim is “cure” (timing)
• Duration dependent on surgery and availability of highly orally bio-available agents
  – Resistance
  – Drug interactions (including QTc)
• OPAT use is safe: Follow Good Practice Recommendations for OPAT
• IV Beta lactams probably more effective than GPs
• “Equipoise” in IV vs oral for longer term Rx
New Developments
<table>
<thead>
<tr>
<th>OPAT trends over 10 yrs in NHS GGC</th>
<th>Trend over time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Referral from non-local hospital</td>
<td>$X^2_{\text{trend}} = 72.92$ $p &lt; 0.0001$</td>
</tr>
<tr>
<td>Referral from secondary care</td>
<td>$X^2_{\text{trend}} = 26.07$ $p &lt; 0.0001$</td>
</tr>
<tr>
<td>Co-morbidity</td>
<td>$X^2_{\text{trend}} = 24.07$ $p &lt; 0.0001$</td>
</tr>
<tr>
<td>Non-SSTI infection</td>
<td>$X^2_{\text{trend}} = 97.14$ $p &lt; 0.0001$</td>
</tr>
<tr>
<td>MRSA infections (as % of S. aureus)</td>
<td>$X^2_{\text{trend}} = 6.682$ $p = 0.0097$</td>
</tr>
<tr>
<td>G-ve infections (% of +ve cultures)</td>
<td>$X^2_{\text{trend}} = 10.491$ $p = 0.0012$</td>
</tr>
<tr>
<td>Self / carer antibiotic admin</td>
<td>$X^2_{\text{trend}} = 48.49$ $p &lt; 0.0001$</td>
</tr>
</tbody>
</table>

Barr et al, IJAA 2012
ESBL Resistant E. coli Implant infections

**Tigecycline**

**Gent 4 xs MIC**

**Fosfomycin**

**Colistin**

**FIG 1** Time-kill curves with 0.5, 1, and 4x the MIC of tigecycline (TIG), colistin (COL), fosfomycin (FOS), and gentamicin (GEN) against E. coli in log growth phase (inoculum, 10⁶ CFU/ml). Values are means ± SD. The experiments were performed in triplicate. GC, growth control.

Corvec et al, AAC, 2013; 57: 1421
Synergy between Fosfomycin and Colistin

**FIG 2** Time-kill curves with 0.5× the MIC of tigecycline (TIG), colistin (COL), fosfomycin (FOS), and gentamicin (GEN) in combinations against *E. coli* in log growth phase (inoculum, 10⁶ CFU/ml). Values are means ± SD. The experiments were performed in triplicate. GC, growth control.

Corvec et al, AAC, 2013; 57: 1421
Growth during Rx and 5 days post Rx

FIG 3 Activities against planktonic bacteria in cage fluid aspirated during treatment (i.e., day 5; open bars) and 5 days after end of treatment (i.e., day 10; closed bars). In each group, fluid from 12 cages (from 3 animals) was investigated. The y axis shows log_{10} CFU/ml in aspirated cage fluid, expressed as means ± standard deviations (SD).

Corvec et al, AAC, 2013; 57: 1421
Background

• c.180 K TKR or THRs / year in UK
  – 14 K in Scotland (2013)
• c. 0.5-5% of all joint replacements Hip > knee
• Diagnosis
  – Acute post-op vs Acute infection of established prosthesis: Heat, erythema, pain, swelling +/-wound
  – Sub-acute: pain and radiological loosening
• Multiple tissue sampling w/o contamination
  – Sonication (when available)
  – Microbiological (PCR when available)
  – Histological
Common organisms

- *Staph. aureus* inc MRSA (40.6%)
- Coagulase negative staphylococci (15.9%)
- Coliforms (15.6%)
- Enterococci (9.6%)
- Streptococci
- Diphtheroids
- Pseudomonas
- Anaerobes
- Polymicrobial

*(Fifth Report of the Mandatory Surveillance of Surgical Site Infection in Orthopaedic Surgery)*
Decline in inpatient SSI in TKR and TKR in Scotland

Hip arthroplasty enhanced SSI surveillance:
0.76% by day 30
Majority are deep seated SSI

SSHAIP, HPS, 2014
Fosfomycin + Colistin: Cure in biofilm

**FIG 4** Rate of cure of cage-associated infection. The values are numbers of cage cultures without growth of *E. coli* divided by the total number of cages in the treatment group (*n* = 12). Significant differences compared to untreated controls are indicated with asterisks (*, P < 0.05; **, P < 0.01).
Pharmacokinetic parameters of daptomycin at steady-state (Day 4 or 5) from 9 patients with diabetic foot infections treated with 6 mg/kg daptomycin

<table>
<thead>
<tr>
<th></th>
<th>Cmax (mg/l)</th>
<th>Half life (h)</th>
<th>AUC₀-24*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>72.9</td>
<td>10.05</td>
<td>619.30</td>
</tr>
<tr>
<td>Subcutis inflamed</td>
<td>4.0</td>
<td>10.98</td>
<td>54.47</td>
</tr>
<tr>
<td>Metatarsal bone</td>
<td>4.7</td>
<td>10.72</td>
<td>60.24</td>
</tr>
</tbody>
</table>

* Steady state concentrations at baseline were used for concentrations at 24 hours

• The EUCAST breakpoint for staphylococci is 1 mg/L