Role of IV Therapy in Bone and Joint Infection

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Queen Elizabeth University Hospital
Lead Doctor Antimicrobial Management Team,
NHS GGC
@raseaton66
Lilian Chiwera @lilian_c... · 18/10/2017
Conclusion from #OVIVA trial #QIST2017

PO is non-inferior to IV antibiotic therapy in the treatment of bone and joint infection.

- Good for the health economy
  - Estimated cost saving to the NHS of >£30M
  - Estimated US savings PJI hip and knee >$140M

estee @EsteeTorok · 23/04/2017
Oral antibiotics non-inferior to IV antibiotics in bone and joint infections
@mattscarborough #OVIVA #ECCMID2017

Annie Joseph @ajosep... · 12/06/2017
Take away messages for me, #OVIVA publication may be paradigm shift??
@BSACandJAC #antibioticaction @AntibioticLeeds

Michael Marks @dr_mi... · 22/04/2017
D1S5 #ECCMID2017 #BreakingRCTs #OVIVA study bone&joint infection. PO non-inferior to IV even in worst case sensitivity analysis. Impressive

David Jenkins @DafyddSiencyns

Does the OVIVA trial spell the end of OPAT? #ECCMID2017 @raseaton66
22/04/2017, 17:35

Repeating to @raseaton66 and @DafyddSiencyns

Time to reel in the over-hyped and expensive OPAT. Let's do more tabs. Thank you OVIVA!
The “IVnOAT” Perspective

“I’m afraid you’ve had a paradigm shift.”
What is the role of OPAT?

- To improve quality and efficiency of care and reduce risk of harm in patients with infection who would otherwise be hospitalised for IV antibiotic therapy
  - Infection specialist influence in the broader patient population
  - Essential component of the modern integrated, interdisciplinary infection service
  - More efficient and appropriate use of inpatient resource – part of the Antimicrobial Stewardship strategy
What OPAT is not

- An alternative to thoughtful person-centred medical care (or a good debridement)
- An easy or cheap option (long term implant failure)
- Safer (than oral Rx)
- Better (than oral Rx all the time)
OPAT is part of an Antimicrobial Stewardship (AMS) Strategy

• Start SMART then FOCUS
  – Review the clinical diagnosis + continuing need for antibiotics at 48*-72 hours
  – Document a clear plan of action:
    • Stop antibiotics if there is no evidence of infection
    • Switch antibiotics from IV to oral
    • Change antibiotics: narrower spectrum or broader if required
    • Continue + document next review / stop date

Start Smart - Then Focus Antimicrobial Stewardship Toolkit for English Hospitals, PHE, Updated March 2015
OPAT and BJI GGC Experience

86.4% success on completion of OPAT
70.2% success-up to 2 years FU

Figure 1. Kaplan-Meier survival estimate of time to treatment failure for all patients showing all follow-up data available.

MacKintosh, White, Seaton, J Antimicrob Chemother 2011
OVIVA STUDY

• 1054 randomised

• **Primary Treatment success (all comers)** 86% @ 1 year

• Shorter hospitalisation/costs in oral Rx

• Less line-related complications in oral Rx
We should definitely use oral therapy when it is safe and effective to do so.. But does that mean all the time?
OVIVA - Important caveats

• Patients with SAB were excluded
• If no oral (or IV) regimen available - excluded
• MDR infections (Gram positive and negative) and significant potential DDIs likely to have limited oral options and led to some exclusions
• Carefully constructed oral regimens with close monitoring (ECGs, Bloods) and other drug modification by specialists supervising Rx
## Risk of failure by surgical procedure and route of Rx

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>OR</th>
<th>95% CI</th>
<th>N in each group</th>
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<td>OM debrided (no implant)</td>
<td>0.93</td>
<td>(0.45, 1.94)</td>
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<td>OM not debrided (no implant)</td>
<td>0.34</td>
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<tr>
<td>DAIR</td>
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<td>Removal of implant</td>
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<td>(0.34, 1.23)</td>
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<td>1 stage revision</td>
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<td>(0.58, 8.00)</td>
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</table>

Scarborough et al, ECCMID, 2017
## Risk of failure by infecting pathogen and route of Rx

<table>
<thead>
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<th>Subgroup</th>
<th>OR</th>
<th>95% CI</th>
<th>N in each subgroup</th>
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<tr>
<td>S. aureus</td>
<td>0.89</td>
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<tr>
<td>Pseudomonas</td>
<td>n/a</td>
<td>n/a</td>
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<tr>
<td>Other GNR</td>
<td>1.13</td>
<td>(0.43, 2.97)</td>
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<tr>
<td>Strep. species</td>
<td>0.54</td>
<td>(0.19, 1.55)</td>
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<tr>
<td>CNS</td>
<td>0.56</td>
<td>(0.24, 1.32)</td>
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<tr>
<td>None identified</td>
<td>1.91</td>
<td>(0.77, 4.75)</td>
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</table>

Scarborough et al, ECCMID, 2017
Risk of failure by planned antibiotics (excluding rifampicin)

No statistically significant difference in outcome by planned antibiotic choice

Scarborough et al, ECCMID, 2017
Suggests IV Rx may be preferred/more evidence required when

- SAB-related
- One stage revision
- No positive microbiology
- Organisms where there are limited oral options
  - Pseudomonas, Cipro R GNs
  - MDRGPos infections
Infected MW elbow

3 months Rx planned

Clinical Infectious Diseases; 2013; 56: 1-25
Infected MW elbow MDRCNS

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Gram Film: White cells +
No Bacteria Seen

CULTURE RESULT:  

GROWTH:

a) Staphylococcus epidermidis  
b)  
c)  
d)  
e)  
f)  

ANTIBIOTIC  a) b) c) d) e) f)
Clindamycin  R  
 Clarithromycin  R  
 Fusidic Acid  R  
 Flucloxacinilin  R  
 Rifampicin  R  
 Vancomycin  S  
 Trimethoprim  R  

Tests included in UKAS Accreditation (8078) Scope.
Infected MW elbow MDRCNS

Gram Film: White cells +
No Bacteria Seen

CULTURE RESULT: GROWTH:
a) Staphylococcus epidermidis Light
b) c) d) e) f)

ANTIBIOTIC a) b) c) d) e) f)
Clindamycin R
Clarithromycin R
Fusidic Acid R
Flucloxacillin R
Rifampicin R
Vancomycin S
Trimethoprim R

Tests included in UKAS Accreditation (8078) Scope.

OP Rx OPTIONS
Daptomycin
Teicoplanin
Linezolid
Linezolid - considerations

• DDI - Toxicity
  • SSRIs and MAOI and Serotonin syndrome -after 4 days (1-20 days)
• DDI – Loss of efficacy
  • Rifampicin - reduced [Linezolid]
• Myelotoxicity (TCP -10%, anaemia – 30%) in prolonged Rx
• Lactic acidosis
• Optic neuropathy (reversible) blindness
• Peripheral neuropathy. (10 days to 6 months) – often irreversible

Linezolid – GGC OPAT Strategy

• Avoid if on SSRI or MAOI (serotonin syndrome)
• Additional caution if CKD
• Limit to final 4 weeks of therapy
• Monitor weekly (FBC, LFTs, lactate) and warn re visual change and neuropathy
• Co-prescribe B6 with all
• DDIs - Do not co-prescribe with: Rifampicin and allow at least one week “wash out” if prior Rifampicin

Gebhart BC et al *Pharmacotherapy* 2007; 27: 476-9)
**Infected MW elbow MDRCNS**

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**Gram Film:** White cells +  
No Bacteria Seen

**CULTURE RESULT:**

<table>
<thead>
<tr>
<th>ANTIBIOTIC</th>
<th>a)</th>
<th>b)</th>
<th>c)</th>
<th>d)</th>
<th>e)</th>
<th>f)</th>
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<td>R</td>
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<td>Fusidic Acid</td>
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<tr>
<td>Rifampicin</td>
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<tr>
<td>Vancomycin</td>
<td>S</td>
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<tr>
<td>Trimethoprim</td>
<td>R</td>
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</table>

**OP Rx**

Daptomycin for 6 weeks  
Then  
Linezolid for 6 weeks

Tests included in UKAS Accreditation (8078) Scope.
Infected THR post 1-Stage Revision
Infected THR washed out and retained: Polymicrobial infection

Gram Film: No white cells seen
   Gram-Negative Bacilli ++
   Gram-Positive cocci +

CULTURE RESULT:
   a) Klebsiella oxytoca
   b) Enterococcus faecalis
   c) Staphylococcus aureus
   d) 
   e) 
   f)

GROWTH:
   Heavy
   Light
   Heavy

ANTIBIOTIC  a)  b)  c)  d)  e)  f)
Amp/Amoxicillin  R  S
Vancomycin      S  S
Co-amoxiclav    S
Ciprofloxacin   S  S
Gentamicin      S  S
Temocillin      S
Flucloxacillin  
Rifampicin      S

Tests included in UKAS Accreditation (8078) Scope.
Polymicrobial infection – oral options

• E.coli
  – Oral option limited to Ciprofloxacin/Levofloxacin
  – DDIs: SSRIs (QTc prolongation), Cations (chelation and reduced absorption)

• Enterococcus
  – Amoxicillin: Poor bone penetration (oral)
  – Linezolid: Duration limited by toxicity and DDIs
Infected THR washed out and retained

Cipro + Daptomycin + Rifampicin
For first 6 weeks
Then
stop Rifampicin during last week
Start Linezolid for final 6 weeks

Symptomatic CPK rise
Switched early to Linezolid
Developed bilateral foot paraesthesia
Switched to teicoplanin

Gram Film: No white cells seen
Gram-Negative Bacilli ++
Gram-Positive cocci +

CULTURE RESULT:

a) Klebsiella oxytoca
b) Enterococcus faecalis
c) Staphylococcus aureus
d)
e)
f)

GROWTH:
Heavy
Light
Heavy

ANTIBIOTIC  a)  b)  c)  d)  e)  f)
Amp/Amoxicillin  R  S
Vancomycin      S  S
Co-amoxiclav    S
Ciprofloxacin   S  S
Gentamicin      S  S
Temocillin      S
Flucloxacillin  S
Rifampicin      S

Tests included in UKAS Accreditation (8078) Scope.
Levofloxacin + Citalopram
Levofloxacin and Citalopram both increase QTc interval. Use Caution/Monitor. ECG monitoring is recommended, along with drugs that may prolong the QT interval.
Other emerging issues

• Beta Haemolytic Streptococcal infections
  – Increasing resistance to doxycycline and clindamycin
  – Co-morbidity and DDIs

• MDRGNB (Cipro R) infections – No effective oral options
## Oral Antibiotics in BJI - Considerations

<table>
<thead>
<tr>
<th>Oral Antibiotic</th>
<th>MRSA</th>
<th>CNS</th>
<th>Bone Penetration</th>
<th>Biofilm activity</th>
<th>QTc prolong</th>
<th>Other DDIs</th>
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<tbody>
<tr>
<td>Penicillins</td>
<td>X</td>
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<tr>
<td>Clindamycin</td>
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<tr>
<td>Linezolid</td>
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<tr>
<td>Doxycycline</td>
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<tr>
<td>Rifampicin</td>
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<tr>
<td>Sodium fusidate</td>
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<tr>
<td>Quinolones</td>
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...and don’t forget Tolerability, Allergy and Compliance
BJI Rx via OPAT and mean duration of IV Rx (n= 1596)

Duration (days)
Number

2017 (to August)
88 completed Rx
Mean duration 20 days
Oral Antibiotics in BJI GGC OPAT (to August 2017)
OVIVA: implications for service – what we have noticed

• More complex screening of referrals
  – More recommended to switch to oral Rx

• More monitoring of complex oral regimens (especially linezolid, quinolone interactions and QTc monitoring)

• Greater turn over of patients – increased numbers and shorter duration of IV

• More toxicity/ tolerability – esp. lacticacidosis and haematological (TCP, anaemia), diarrhoea and nausea
Orthopaedics

• Empirical Rx will remain IV e.g. Vancomycin following first stage revision/ debridement
• Complicated by SAB – min 2 weeks IV (review individually)
• Option 1
  – Wait for final micro before finalising antibiotic plan
  – Delays OPAT training for a few but potentially more will be discharged earlier on oral Rx
• Option 2
  – Refer and commence OPAT with de-escalation to oral Rx when micro results are confirmed (as OP)
  – Potential for wasted OPAT team resource
• OPAT team provide FU for those who require close toxicity monitoring (e.g. Linezolid)
From OPAT to COPAT: The Complex OP OP Antibiotic Team
OPAT/COPAT MDT (n=42)

BJI (n=28)

ORAL
Linezolid 4/7

INTRAVENOUS
Micro 5 (+ DDIs in 4)
DDIs 2
Oral Failure 3
Other 6

IV
Oral
IVOST
OIVST
Stop
Hosp
Expanding Roles within OPAT team

• Critical role of Antimicrobial Pharmacist in decisions re antibiotic selection
• Increased focus on short term IV Rx and admission avoidance / ambulatory care
  – Cellulitis
  – Pyelonephritis/ urosepsis
• Increasingly complex MDR infections (including CROs)

• Nursing stewardship developments
  – IVOST
  – Nurse educators
  – Independent prescribers
  – Penicillin allergy
FINAL THOUGHTS......
Antibiotics and the Microbiome

• The Microbiome:
  – 100 trillion microbes: 10 x s number of Human cells
• Infinite opportunities for R
• Pressure or Volume (course duration x no. of courses) key in selecting for R
• Nature of Microbiome is central to C. diff risk
Antibiotic Choice & Admin Route and Clostridium difficile (CDI) Risk in OPAT

• Cephalosporin use restricted in hospitals due to high risk of CDI...... but not in OPAT

• Despite higher use of IV cephalosporins in OPAT, UK OPAT cohort studies suggest much lower rates of Clostridium difficile (0.05 per 1000 OPAT days) compared to hospitalised patients.

Risk of CDI and cumulative community antibiotic exposure in prior 6 months

Kavanagh et al JAC;2017; 72 Pages 1193–1201, https://doi.org/10.1093/jac/dkw528
Antibiotic Administration Routes Significantly Influence the Levels of Antibiotic Resistance Microbiota

Lu Zhang, Ying Huang, Yang Zhou, Timur Shirzad, and Ananth Gopinath

Oral administration of antibiotics has been shown to affect the gut microbiota, potentially altering antibiotic resistance patterns. This study explores how different antibiotic administration routes (oral versus intravenous) influence the microbiota and antibiotic resistance. Exposure to antibiotics was associated with changes in the gut microbiota, with oral administration leading to more significant shifts in antibiotic resistance profiles compared to intravenous administration. The study suggests that the route of antibiotic administration can significantly impact the selection of antibiotic-resistant bacteria, highlighting the importance of considering delivery methods in antibiotic therapy.

Additional findings included:

- Oral administration of antibiotics is more likely to expose the gut to a broader range of bacterial populations, potentially increasing the likelihood of selecting antibiotic-resistant strains.
- Intravenous administration, while effective in delivering antibiotics to the bloodstream, may not optimally reach the gut, where most antibiotics are effective.
- The use of alternative antibiotic administration methods, such as dual therapy (oral and intravenous), may help mitigate the selection of antibiotic-resistant bacteria.

These findings underscore the need for careful consideration of antibiotic administration routes to minimize the development of antibiotic resistance.
Conclusions – OVIVA study

• Greater confidence in oral Rx/IVOST but:
  – (suspected) sensitive organism
  – Consideration of DDIs
  – Well organised toxicity monitoring programme

• IV still required for significant proportion of patients
  – MDR
  – DDIs
  – Minimising toxicity, improving tolerability (compliance)

• Need to consider and monitor ecological impact of prolonged oral Rx on gut microbiota (CDI, AMR)

• Critical importance of infection specialist/ COPAT team control on antibiotic choice, route and duration