Tabs or Jabs?
Does it make a difference in the treatment of bone and joint infection?

M Scarborough, HK Li, I Rombach and R Zambellas for the OVIVA network

No conflicts of interest to declare
Background

• Within NHS per year
  • 250,000 joints & fracture procedures
    ➢ ~6300 post-operative infections
    ➢ ~5000 diabetic foot osteomyelitis
  • Cost £20,000 – £40,000 per patient

• Current Practice
  • Prolonged, high dose, IV antibiotics
is rarely controlled without the combination of careful, complete surgical debridement and prolonged (four to six weeks) parenteral antibiotic therapy at high dosage.
<table>
<thead>
<tr>
<th>Study</th>
<th>PO / IV</th>
<th>N</th>
<th>PO (%)</th>
<th>IV (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocarditis Heldman ‘96</td>
<td>Cip+Rif / Oxacillin</td>
<td>44</td>
<td>95</td>
<td>88</td>
<td>0.6</td>
</tr>
<tr>
<td>Spontaneous Bacterial Peritonitis Navasa ‘96</td>
<td>Oflox / Cefotaxime</td>
<td>123</td>
<td>84</td>
<td>85</td>
<td>1.0</td>
</tr>
<tr>
<td>Skin and Soft Tissue Infection (MRSA) Weigelt ‘05</td>
<td>Linezolid / Linezolid</td>
<td>592</td>
<td>91.2</td>
<td>93.5</td>
<td>0.34</td>
</tr>
<tr>
<td>Community Acquired pneumonia (Paeds) Atkinson ‘07</td>
<td>Amox / Benpen</td>
<td>246</td>
<td>97</td>
<td>96</td>
<td>n/a</td>
</tr>
<tr>
<td>Perforated appendix Adibe ‘08</td>
<td>Co-T / Amp-sulbactam</td>
<td>149</td>
<td>96</td>
<td>86</td>
<td>0.08</td>
</tr>
<tr>
<td>Febrile neutropenia Gupta ‘09</td>
<td>Oflox+Amox / Ceftriax</td>
<td>123</td>
<td>90</td>
<td>93</td>
<td>0.74</td>
</tr>
<tr>
<td>S. aureus osteomyelitis Euba ‘09</td>
<td>Co-T + Rif / Cloxacillin</td>
<td>42</td>
<td>92</td>
<td>94</td>
<td>1.0</td>
</tr>
<tr>
<td>Osteomyelitis (Cochrane) Conterno ‘09</td>
<td>Various / Various</td>
<td>180</td>
<td>82</td>
<td>80</td>
<td>1.0</td>
</tr>
</tbody>
</table>

“The main finding of this review is the lack of evidence to inform practice.”
So......

• No clear evidence that IV antibiotic therapy is superior

• No clear evidence that oral antibiotic therapy is inferior

• Variation in practice

→ OVIVA – a non-inferiority RCT
OVIVA Trial design

• Pragmatic – open label, **oral vs IV for first 6/52**

• Antibiotic selection by an infection specialist

• No trial specific samples / investigations / clinics

• Wide data point margins (@ ~ 6/52, 4/12, 1 yr)

• Follow up - 1 year

• Hard end points
Inclusion / Exclusion

- A clinical syndrome comprising any of the following; a) localized pain OR b) localized erythema OR c) temperature >38.0°C OR d) a discharging sinus or wound AND
- willing and able to give informed consent AND
- aged 18 years or above AND
- the patient has received 7 days or less of intravenous therapy after an appropriate surgical intervention to treat bone or joint infection (regardless of pre-surgical antibiotics) or, if no surgical intervention is required, the patient has received 7 days or less of intravenous therapy after the start of the relevant clinical episode.
- has a life expectancy > 1 year AND
- has a bone and joint infection in one of the following categories: a) Native osteomyelitis (i.e., bone infection without metalwork) including haematogenous or contiguous osteomyelitis, and long bone, skull, foot or other foci OR b) Native joint sepsis treated by excision arthroplasty OR c) Prosthetic joint infection treated by debridement and retention, by one stage revision or by implantation of the prosthetic joint (with or without planned re-implantation) OR d) Orthopaedic device or bone-graft infection treated by debridement and retention, or by debridement and removal OR e) Spinal infection including discitis, osteomyelitis and/or epidural abscess.
- Staphylococcus aureus bacteraemia on presentation or within the last 1 month OR
- bacterial endocarditis on presentation or within the last month (NB there are no study mandated investigations. Participants are not required to have echocardiograms, blood cultures, or any other investigations to exclude endocarditis in the absence of a clinical indication) OR
- Any other concomitant infection which, in the opinion of the clinician responsible for the patient, required a prolonged intravenous course of antibiotics (e.g. mediastinal infection or central nervous system infection) OR
- Mild osteomyelitis, defined as osteomyelitis which, in the opinion of the clinical investigator, would not usually require a 6 week course of intravenous antibiotics OR
- Any infection for which there are no suitable antibiotic choices to permit randomization between the two arms of the trial (for instance, where organisms are only sensitive to intravenous antibiotics, which occurred in <5% of patients during recruitment for our pilot study) OR
- Previous enrolment in the trial OR
- Septic shock or systemic features requiring intravenous antibiotics in the opinion of the treating clinic (the patient may be re-evaluated if these features resolve) OR
- The patient is unlikely to comply with trial requirements following randomization (including specific requirement for PO or IV course) in the opinion of the investigator OR
- There is clinical, histological or microbiological evidence of mycobacterial, fungal, parasitic or viral aetiology OR
- The patient is receiving an investigational medical product as part of another clinical trial.

Consenting adults

Bone, joint or metalware infection

Has had < 7 days IV therapy

Needs IVs for other reasons
(e.g. Staph bacteraemia, IE, severe sepsis)

No oral option

Wouldn’t normally get 6/52 antibiotics
End points

• **Primary – definite treatment failure***
  – Bacteriological, histological, clinical
• **Secondary**
  – SAEs
  – Line complications
  – Probable or possible treatment failure***
  – Early termination of randomised route
  – Resource utilisation
  – PROMs (EQ-5D, Oxford hip and knee scores)

* All potential treatment failures were reviewed by blinded endpoint committee using **redacted notes**
Typical cases

• Single stage, 1st stage or DAIR for PJI
• Long bone osteomyelitis
• Infected orthopaedic metalware
• Discitis/spinal osteomyelitis
• Diabetic foot osteomyelitis

i.e. ~ any ‘6 weeker’
Participating centres

- Birmingham Heartlands
- Blackpool
- Brighton and Sussex
- Bristol Royal Infirmary
- Cambridge
- Gartnavel General
- Guys and St Thomas’ Hospitals
- Hull Royal Infirmary
- Kings Lynn
- Leeds Teaching Hospitals
- Maidstone
- Medway Maritime, Kent
- Newcastle
- Norfolk and Norwich
- Northampton
- Northumbria
- North West London
- North Staffordshire
- Oxford
- Royal Cornwall, Truro
- Edinburgh
- Royal Free + RNOH, London
- Royal Hallamshire, Sheffield
- Liverpool University Hospital
- University Hospital, North Staffs
- Tayside, Dundee
- Tunbridge Wells
- University College Hospital, London
- Wittington
Enrolment

Not randomised (n=249)
- Prefer IVs (n=72)
- Prefer POs (n=44)
- OPAT out of area (n=19)
- Doctors not in agreement (n=6)
- Left to go abroad (n=10)
- Transferred to another hospital (n=8)
- Other (n=49)
- Declined without providing further reason (n=187)

Assessed for eligibility (n=2077)

Not eligible (n=628)
- Staph aureus bacteraemia (n=54)
- Bacterial endocarditis (n=29)
- Concomitant infection mandating IV therapy (n=43)
- Mild disease requiring <6/52 antibiotics (n=182)
- No suitable PO regimen available (n=80)
- Previous enrolment in the trial (n=10)
- Shock or other features mandating long IV therapy (n=28)
- Unlikely to comply with trial requirements (n=74)
- Mycobacterial, fungal, parasitic or viral aetiology (n=6)
- Receiving an investigational product in another trial (n=0)
- Reasons not reported (n=122)

Eligible (n=1449)

Randomised (n=1054)

Allocated to IV (n=527)
Received at least 4 weeks of their allocated strategy (n=458)

Allocated to PO (n=527)
Received at least 4 weeks of their allocated strategy (n=478)
Allocated to IV (n=527)
Received at least 4 weeks of their allocated strategy (n=458)

Lost to follow-up (n=22)
Reasons:
- Patient withdrew from trial (n=7)
- Patient was lost to follow-up (n=5)
- Patient died* (n=10)

Analysed (intention to treat) in primary analysis (n=527)
Excluded from the primary analysis (n=0)

Excluded from per protocol (n=84):
- Endpoint data missing (n=15)
- Less than 4 weeks of allocated strategy for reasons other than possible or probably recurrence (n=63)
- Both (n=6)

Analysed in per protocol analysis (n=443)

Allocated to PO (n=527)
Received at least 4 weeks of their allocated strategy (n=478)

Lost to follow-up (n=20)
Reasons:
- Patient withdrew from trial (n=7)
- Patient was lost to follow-up (n=7)
- Patient died* (n=6)

Analysed (intention to treat) in primary analysis (n=527)
Excluded from the primary analysis (n=0)

Excluded from per protocol (n=61):
- Endpoint data missing (n=13)
- Less than 4 weeks of allocated strategy for reasons other than possible or probably recurrence (n=43)
- Both (n=5)

PP n=909

Analysed in per protocol analysis (n=466)
Baseline Summaries

• Clinical presentation
• Surgical procedure
• Site of infection
• Organism isolated
• Histological diagnosis
• Local antibiotic use
• Co-morbidities

Evenly matched

Figure 3. Bones Involved in Hematogenous Osteomyelitis.
Proportion of participants on IV antibiotics (to day 60)
Forest plot of risk differences (95% CI) for definitive treatment failure (PO vs. IV)

<table>
<thead>
<tr>
<th></th>
<th>IV (527)</th>
<th>PO (527)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx failure</td>
<td>74 (14.04%)</td>
<td>67 (12.71%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>IV (506)</th>
<th>PO (509)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx failure</td>
<td>74 (14.62%)</td>
<td>67 (13.16%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>IV (443)</th>
<th>PO (466)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx failure</td>
<td>69 (15.58%)</td>
<td>61 (13.09%)</td>
</tr>
</tbody>
</table>

(Worst case sensitivity analysis for missing data: Risk difference (PO-IV) = 2.09% and 90% CI: (-1.54, 5.71))
Time to treatment failure by randomised treatment strategy

Kaplan-Meier curves: treatment failure free survival

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>IV</th>
<th>PO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>523</td>
<td>525</td>
</tr>
<tr>
<td>477</td>
<td>481</td>
<td></td>
</tr>
<tr>
<td>455</td>
<td>462</td>
<td></td>
</tr>
<tr>
<td>425</td>
<td>431</td>
<td></td>
</tr>
<tr>
<td>119</td>
<td>138</td>
<td></td>
</tr>
</tbody>
</table>
Time to permanent discontinuation of antibiotics

Proportion of participants on antibiotic

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>IV</th>
<th></th>
<th>PO</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>523</td>
<td>395</td>
<td>129</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>526</td>
<td>410</td>
<td>120</td>
<td>41</td>
</tr>
</tbody>
</table>

Days from randomisation

- IV
- PO
### Odds ratios for treatment failure by infecting pathogen (PO/IV)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>OR</th>
<th>95% CI</th>
<th>N in each subgroup</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>0.89</td>
<td>(0.49, 1.59)</td>
<td>370</td>
</tr>
<tr>
<td>Pseudomonas</td>
<td>n/a</td>
<td>n/a</td>
<td>32</td>
</tr>
<tr>
<td>Other GNR</td>
<td>1.13</td>
<td>(0.43, 2.97)</td>
<td>116</td>
</tr>
<tr>
<td>Strep. species</td>
<td>0.54</td>
<td>(0.19, 1.55)</td>
<td>81</td>
</tr>
<tr>
<td>CNS</td>
<td>0.56</td>
<td>(0.24, 1.32)</td>
<td>189</td>
</tr>
<tr>
<td>None identified</td>
<td>1.91</td>
<td>(0.77, 4.75)</td>
<td>227</td>
</tr>
</tbody>
</table>
### Odds ratios for treatment failure by surgical procedure

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>OR</th>
<th>95% CI</th>
<th>N in each group</th>
</tr>
</thead>
<tbody>
<tr>
<td>OM debrided (no implant)</td>
<td>0.93</td>
<td>(0.45, 1.94)</td>
<td>318</td>
</tr>
<tr>
<td>OM not debrided (no implant)</td>
<td>0.34</td>
<td>(0.08, 1.41)</td>
<td>76</td>
</tr>
<tr>
<td>DAIR</td>
<td>1.20</td>
<td>(0.61, 2.34)</td>
<td>237</td>
</tr>
<tr>
<td>Removal of implant</td>
<td>0.65</td>
<td>(0.34, 1.23)</td>
<td>297</td>
</tr>
<tr>
<td>1 stage revision</td>
<td>2.16</td>
<td>(0.58, 8.00)</td>
<td>87</td>
</tr>
</tbody>
</table>
Odds ratios for failure by planned antibiotics (excluding rifampicin)

No statistically significant difference in outcome by planned antibiotic choice
Odds ratios for treatment failure by planned use of Rifampicin

Odds ratios (95% CI) for definitive treatment failures by planned rifampicin in planned IVs (PO/IV)

Odds ratios (95% CI) for definitive treatment failures by planned rifampicin inclusion in planned POs (PO/IV)
## Serious adverse events / line complications

<table>
<thead>
<tr>
<th></th>
<th>Intravenous arm (IV) (N = 527)</th>
<th>Oral arm (PO) (N = 527)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAEs reported</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 SAE</td>
<td>109 (20.68%)</td>
<td>89 (18.79%)</td>
</tr>
<tr>
<td>&gt; 1 SAE</td>
<td>37 (7.02%)</td>
<td>49 (9.30%)</td>
</tr>
<tr>
<td><strong>Line complications</strong></td>
<td>49</td>
<td>5</td>
</tr>
<tr>
<td>Mechanical failure</td>
<td>24 (48.98%)</td>
<td>3 (60.00%)</td>
</tr>
<tr>
<td>Thrombophlebitis/ thrombosis</td>
<td>13 (26.53%)</td>
<td>1 (20.00%)</td>
</tr>
<tr>
<td>Infection</td>
<td>12 (24.49%)</td>
<td>1 (20.00%)</td>
</tr>
<tr>
<td>Line removed</td>
<td>42 (85.71%)</td>
<td>4 (80.00%)</td>
</tr>
</tbody>
</table>
EQ-5D-3L Index over time by treatment arm

Mobility
Self care
Usual activities
Pain/discomfort
Anxiety/depression
VAS ‘Health status’
Intravenous arm (IV) (N = 508)
Oral arm (PO) (N = 508)
Total (N = 1016)

Median length of stay (IQR)
14 (11, 21)  
11 (8, 20)  
13 (9, 21)
## Cost effectiveness results

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Intravenous Mean (SE)</th>
<th>Oral Mean (SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total non-surgical costs to one year</td>
<td>£13,274 (£446)</td>
<td>£10,534 (£453)</td>
</tr>
<tr>
<td>Total QALYs</td>
<td>0.537 (0.013)</td>
<td>0.545 (0.015)</td>
</tr>
<tr>
<td>Incremental costs</td>
<td>£2,740 (£638)</td>
<td></td>
</tr>
<tr>
<td>Incremental QALYs</td>
<td>0.008 (0.020)</td>
<td></td>
</tr>
</tbody>
</table>

(QALY ranges form 0 to 1, where 0 is dead and 1 is a year in perfect health)
Limitations

• Open label – blinded end point committee

• Heterogeneity of participants – randomised

• Antibiotic selection – infection specialist

• Follow-up to one year – pragmatic
Conclusions

Oral therapy is non-inferior as compared to IV therapy when used in the early treatment of bone and joint infection.

• Good for patients
  – Early discharge from hospital
  – Convenience, independence and autonomy over treatment

• Good for practice
  – Reduced risks associated with IV lines
  – Antimicrobial stewardship

• Good for the health economy
  – Estimated cost saving to the NHS of £16-25M
Thanks to all sites, staff, participants and the NIHR

matthew.scarborough@ouh.nhs.uk
Bone Infection Unit
Nuffield Orthopaedic Centre, Oxford
(Poster ID54 – Networking Corner, Hall A)