Hot Topics in Infectious Diseases

CSHP AGM
November 16, 2019
Lesley Palmay, BSc, BScPhm, MSc, ACPR
Clinical Coordinator & ID Pharmacist, Sunnybrook Health Sciences Centre
Disclosures

• Consulting fee:
  • Sunovion Pharmaceuticals

• None relevant to today’s talk
What's Hot?

Partial Oral Therapy for Osteomyelitis: Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Seven Versus 14 Days of Antibiotics for Uncomplicated Gram-Negative Bacterial Infections: A Noninferiority Randomized Trial

CID. 2019;69(7):1091–8

https://clinicaltrials.gov/ct2/show/NCT03005145

NEJM. 2019;380:415-24
NEJM.2019;38(5):487-89
NEJM. 2019;380:425-36
IV or Not IV – That is the Question

• Paradigm shift in Infectious Diseases

• Re-evaluating the need for:
  • Long treatment durations and/or
  • Intravenous Therapy
The Central Dogma of Deep-Seated Infections

Tenant #1: Intravenous
Tenant #2: For a long time (≥ 4-6 weeks)

• Recommendations based on little evidence & derived in an era when pharmacokinetics of oral agents were not considered or well-studied

• IV therapy not without challenges:
  • Longer hospitalizations
  • Complications (e.g. line-related infections /thrombosis)
  • IV drug users

• Some data to suggest that oral therapy may be “just as good” as IV

Endocarditis
Bone & Joint Infections

NEJM.2019;38(5):487-89
NEJM 1970; 282:198-206
Objectives

• Review contemporary data relating to oral therapy for the treatment of Bone and Joint Infections (OVIVA trial) and Infective Endocarditis (POET trial)

• Apply the evidence by the OVIVA and POET trials to a patient case

• Share our experiences with using oral therapy for the treatment of Bone & Joint Infections and Infective Endocarditis
Oral Therapy for Bone & Joint Infections
Study Objective:
To determine whether oral antibiotic therapy is noninferior to intravenous antibiotic therapy for the management of complex orthopedic infections.
OVIVA at a Glance....

• **Study Design**: multicenter, open-label, parallel-group, randomized, controlled non-inferiority study
  - 26 centres in the UK

• **Population**: n = 1054; adults with bone and joint infections
  - **Inclusion**: native OM, native joint infection, prosthetic joint infection, orthopedic fixation device infection, vertebral OM (± diskitis or soft tissue infection)
  - **Exclusion**: IE, *S. aureus* bacteremia, concomitant infection requiring IV therapy, anticipated poor compliance, suspected/confirmed mycobacterial/parasitic/fungal etiology

• **Intervention**:
  - IV vs. oral therapy for entire 6 week course (start of randomly assigned no more than 7 days after surgery or start of antibiotic therapy)
  - Antibiotics at the discretion of ID physician; assumed to be the most appropriate for the patient

• **Primary Outcomes**: definite treatment failure within 1 year of randomization
  - Presence of ≥ 1 clinical criterion (draining sinus tract/frank pus), microbiologic criterion (e.g. identical aspirate/biopsy microbiology), histological criterion (inflammatory infiltrate or microorganisms) *adjudicated by 3 independent & blinded specialists*
Meet the Average Joe (OVIVA Patient)

- 61 year old male
- Relatively healthy (few comorbidities)
- Either chronic osteomyelitis OR retained implant/device
- Growing *Staphylococcus species*
- Excellent patient – 90% medium/high adherence

NEJM. 2019;380:425-36
NEJM. 2019;380:425-36 (Supplementary data)
http://clipartmag.com/person-outline-clipart
Meet the Average Joe (OVIVA Patient)

• 61 year old male
• Relatively healthy (few comorbidities)
• Either chronic osteomyelitis OR retained implant/device
• Growing *Staphylococcus species*
• Excellent patient – 90% medium/high adherence

What was unrepresented?
Older patients
Multiple co-morbidities (T2DM, PVD)
Smokers
Vertebral OM
Pseudomonas (5%)
Gram negatives (20%)
MRSA (19 patients)

NEJM. 2019;380:425-36
NEJM. 2019;380:425-36 (Supplementary data)
http://clipartmag.com/person-outline-clipart
Meet the Average Antibiotic Course

- **Total duration** of therapy ~75 days (~11 weeks)
  - i.e. ~80% of antibiotic courses were extended > 6 weeks

- ~7 days of **IV therapy**, followed by:
  - More IV therapy (IV arm) OR
  - Oral therapy (PO arm)

- Mostly monotherapy (10%)

- Antibiotics:
  - *IV therapy*: **glycopeptides*/cephalosporins* (~70%)
  - *Oral Therapy*: **quinolones*/macrolides*/lincosamides* (~70%)

---

NEJM. 2019;380:425-36
NEJM. 2019;380:425-36 (Supplementary data)
Meet the Average Antibiotic Course

- **Total duration of therapy** ~75 days (~11 weeks)
  - i.e. ~80% of antibiotic courses were extended > 6 weeks

- ~7 days of IV therapy, followed by:
  - More IV therapy (IV arm) OR
  - Oral therapy (PO arm)

- Mostly monotherapy (10%)

- Antibiotics:
  - *IV therapy*: glycopeptides/cephalosporins (~70%)
  - *Oral Therapy*: quinolones/macrolides/lincosamides (~70%)

- Little use of oral beta-lactams (penicillins - 14%)
- Adjunctive rifampin use ≥ 6 weeks greater in PO vs. IV arm (31.4% vs. 22.9%)
### Primary Endpoint: Definitive Treatment Failure

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Oral Group</th>
<th>IV Group</th>
<th>Risk Δ (90% CI; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT</td>
<td>13.3%</td>
<td>14.7%</td>
<td>-1.4% (−4.9 to 2.2%; −5.6 to 2.9%)</td>
</tr>
<tr>
<td>mITT</td>
<td>13.2%</td>
<td>14.6%</td>
<td>-1.5% (−5.0 to 2.1%; −5.7 to 2.8%)</td>
</tr>
<tr>
<td>Per protocol</td>
<td>13.1%</td>
<td>15.6%</td>
<td>-2.5% (−6.3 to 1.3%; −7.0 to 2.1%)</td>
</tr>
<tr>
<td>Worst-Case Sensitivity Analysis</td>
<td>16.1%</td>
<td>14.0%</td>
<td>2.1% (−1.5 to 5.7%; −2.2 to 6.4%)</td>
</tr>
</tbody>
</table>

*Non-inferiority margin initially set at 5%; reset at 7.5% at interim analysis

Met non-inferiority based on **either 7.5% or 5%** margin

Met non-inferiority based on **7.5% margin**

ITT – all randomized participants; missing endpoint data imputed (missing data for 39 patients- 3.7%)
mITT – all participants with complete endpoint data
Per protocol – participants who received at least 4 weeks of randomly assigned patients
Worst Case Sensitivity analysis: any missing data coded as: success (IV arm) and failure (oral arm)
OVIVA: What about those Subgroups?

3 - Infecting pathogen, heterogeneity p = 0.30
- Staphylococcus aureus: 24/153 (0.89, 0.49, 1.59)
- Coagulase negative Staphylococcus: 10/89 (0.56, 0.24, 1.32)
- Streptococcus species: 9/41 (0.54, 0.19, 1.65)
- Gram negative organism(s) (other than Pseudomonas): 10/45, 10/51 (1.13, 0.43, 2.97)
- No infecting pathogen identified: 14/98, 8/107 (1.91, 0.77, 4.75)
- Pseudomonas species: 0/16, 3/13 (Excluded)

5a - Planned RIF in IV regimens, heterogeneity p = 0.85
- Yes: 9/60, 10/63 (0.94, 0.36, 2.49)
- No: 44/298, 64/369 (0.85, 0.56, 1.29)

5b - Planned RIF in PO regimens, heterogeneity p = 0.12
- Yes: 25/234, 32/196 (0.65, 0.38, 1.14)
- No: 41/207, 30/180 (1.19, 0.71, 1.98)

4b - Planned PO treatment, heterogeneity p = 0.80
- Penicillins: 17/57, 9/48 (1.59, 0.65, 3.89)
- Quinolones: 20/189, 26/179 (0.73, 0.39, 1.35)
- Tetracyclines: 7/40, 7/30 (0.75, 0.24, 2.37)
- Macrolides / Lincosamides: 5/53, 6/44 (0.69, 0.20, 2.42)
- Other single IV antibiotic: 8/39, 6/22 (0.75, 0.23, 2.45)
- Combination IV antibiotics: 9/63, 8/53 (0.95, 0.34, 2.62)
OVIVA: What about those Subgroups?

6 - Metal retained, heterogeneity p = 0.13
No metal retained
34/269 43/258
Metal retained
30/132 23/139

8 - Peripheral vascular disease, heterogeneity p = 0.47
Yes
3/23 9/20
No
61/419 65/412

Favours oral
Favours IV
Other Findings: Adverse Events

Serious Adverse Events
• Overall, not significantly different between groups (~27%)
  • IV catheter-related complications: 9.4% (IV arm), 1.0% (oral arm)
  • Gastrointestinal: 9.5% (IV arm), 5.8% (oral arm)
  • *C. difficile*-associated diarrhea: 1.7% (IV arm), 1.0% (oral arm)

Hospitalization-Days
• Significantly longer in the IV vs. oral arm (14 days vs. 11 days; p<0.001)

Cost Effectiveness Analysis:
• Estimated cost savings of ~$3,500 per patient in the oral arm
  • Antibiotic costs, administration of antibiotics (equipment, staff time), hospitalized bed days
We found that appropriately selected oral antibiotic therapy was non-inferior to intravenous therapy when used during the first 6 weeks in the management of bone and joint infection, as assessed by treatment failure within 1 year. Oral antibiotic therapy was associated with a shorter length of hospital stay and with fewer complications than intravenous therapy.
Oral Therapy for Endocarditis
Poet Trial

Study Objective:
To determine whether a shift from intravenous to oral antibiotics would result in efficacy and safety similar to those with continued intravenous treatment in patients with endocarditis of the left-side of the heart.
Poet at a Glance....

• **Study Design:** multicenter, **open-label**, randomized, controlled non-inferiority study
  - Cardiac Centres in Demark

• **Population:** n = 400; adults with **left-sided** bacterial endocarditis
  - **Inclusion:** Adult (≥ 18 years), **stable**, infected with Streptococci, *Enterococcus faecalis*, Staphylococcus aureus or Coagulase-negative staphylococci, ≥ **10 days of appropriate parenteral antibiotic treatment**, T < 38.0 °C > 2 days, CRP < 25% peak value or < 20 mg/L, and white blood cell count < 15 x 10⁹/L during antibiotic treatment, **no abscess**, TTE & TTE within 48 hours of randomization

• **Exclusion:** Body mass index > 40, concomitant infection requiring intravenous antibiotic therapy, inability to give informed consent to participation, suspicion of reduced absorption, **anticipated non-compliance**
Poet at a Glance (cont)....

• **Intervention:**
  - Random assignment ratio to continued IV antibiotic treatment or to a shift to oral therapy
    - In accordance with guidelines of the European Society of Cardiology, Danish Society of Cardiology
  - Oral antibiotics: **moderate to high bioavailability, two antibiotics from different drug classes**
    - with different antimicrobial mechanisms of action and different metabolization
  - **Plasma antibiotic levels** of oral agents were obtained on Day 1 & Day 5; dose adjustments made if necessary

• **Participate follow up:**
  - Oral therapy group: assessed in outpatient clinics, **2-3 times per week** throughout oral treatment phase; **end-of-treatment TEE** (transesophageal echocardiography) to assess sufficient response to treatment
  - Followed at outpatient clinics at 1 week, and at months 1, 3 and 6 months after completion of antibiotic therapy

• **Primary Outcomes:** composite of all-cause mortality, unplanned cardiac surgery, clinically evident embolic events, or relapse of bacteremia with the primary pathogen
  - from randomization through 6 months after antibiotic treatment was completed *adjudicated by blinded cardiologists and ID specialists*
Meet the Average Joe (POET Patient)

- 67 year old male
- 1 comorbidity
- VGS aortic native valve endocarditis
- Did not undergo valve replacement
- Clinically stable
- Able to make frequent outpatient visits/week
Meet the Average Joe (POET Patient)

• 67 year old male
• 1 comorbidity
• VGS aortic native valve endocarditis
• Did not undergo valve replacement
• Clinically stable
• Able to make frequent outpatient visits/week

What was unrepresented:
Prosthetic valve IE (~25%)
Enterococci (~25%)
Staphylococcus (~20%) – NO MRSA
IV drug users (n=5; 1%)

Note: that 80% of patients screened were deemed ineligible (common reasons: expected non compliance, lack of availability to follow-up, elevated inflammatory markers)
Meet the Average Joe (POET Patient)

- 67 year old male
- 1 comorbidity
- VGS aortic native valve endocarditis
- Did not undergo valve replacement
- Clinically stable
- Able to make frequent outpatient visits/week

“Rock solid humans immunologically, who responded immediately to treatment and got better fast”

-Dr. Mark Crislip  
(host of Puscast)
Meet the Average Antibiotic Course

- **Median Duration of therapy:** ~35 days (~ 5 weeks)
- **Median Duration of IV Therapy:** ~ 17 days (> 2 weeks!)
- **Patient Disposition:** 19 days in hospital (~ 3 weeks)
  - In Denmark, IV home therapy is not available

### Pathogen Antibiotic Therapies Used

#### Streptococci [mostly VGS]
- Amoxicillin 1 g QID + fusidic acid
- Amoxicillin 1 g QID + rifampin
- Amoxicillin 1 g QID + moxifloxacin

#### Enterococcus faecalis
- Linezolid + fusidic acid
- Linezolid + rifampin
- Linezolid + moxifloxacin

#### Staphylococcus aureus
- NB. No MRSA
- Linezolid + rifampin
- Linezolid + moxifloxacin
- Moxifloxacin + rifampin
- Moxifloxacin + clindamycin
- Dicloxacillin 1 g QID + rifampin
- Dicloxacillin 1 g QID + fusidic acid

**CNST**

*4 patients crossed over from po → IV; No cross-over from IV → po*
Meet the Average Antibiotic Course

- **Median Duration of therapy:** ~35 days (~5 weeks)
- **Median Duration of IV Therapy:** ~17 days (>2 weeks!)
- **Patient Disposition:** 19 days in hospital (~3 weeks)
  - In Denmark, IV home therapy is not available

**Pathogen Antibiotic Therapies Used**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Antibiotic Therapies Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococci [mostly VGS]</td>
<td></td>
</tr>
</tbody>
</table>
| Amoxicillin 1 g QID + fusidic acid  
| Amoxicillin 1 g QID + rifampin  
| Amoxicillin 1 g QID + moxifloxacin  
| Enterococcus faecalis |  
| Linezolid + fusidic acid  
| Linezolid + rifampin  
| Linezolid + moxifloxacin  
| Staphylococcus aureus  
**NB. No MRSA** |  
| Linezolid + rifampin  
| Moxifloxacin + rifampin  
| Moxifloxacin + clindamycin  
| CNST |  
|  
| Amoxicillin - (very) high dose amoxicillin to compensate for low bioavailability -? GI tolerability  
| Linezolid – bone marrow suppression  
| Fusidic acid - not available in Canada  
| FQs - increasing concern of toxicities of (e.g. aortopathies)  
| Rifampin – not everyone can take (drug interactions, hepatotoxicity)  

*4 patients crossed over from po ➔ IV; No cross-over from IV ➔ po*
POET: Primary Outcome

**Primary outcome:**
12.1% (IV) vs. 9.0% (Oral); $\Delta = 3.1\%$ [95% CI, -3.4 to 9.6; $p = 0.40$]*\(\dag\)

*met non-inferiority criterion of 10% (?in favour of oral therapy)

\(\dag\) robust in sensitivity analysis that accounted for cross-over from oral to IV therapy

<table>
<thead>
<tr>
<th>Component of Primary Outcome</th>
<th>IV Treatment (n=199)</th>
<th>Oral Treatment (n=201)</th>
<th>Risk $\Delta$ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>6.5%</td>
<td>3.5%</td>
<td>3.0% (-1.4 to 7.7)</td>
</tr>
<tr>
<td>Unplanned cardiac surgery</td>
<td>3.0%</td>
<td>3.0%</td>
<td>0% (-3.3 to 3.4)</td>
</tr>
<tr>
<td>Embolic event</td>
<td>1.5%</td>
<td>1.5%</td>
<td>0% (-2.4 to 2.4)</td>
</tr>
<tr>
<td>Relapse of positive blood culture</td>
<td>2.5%</td>
<td>2.5%</td>
<td>0% (-3.1 to 3.1)</td>
</tr>
</tbody>
</table>

NEJM. 2019; 380:415-24
**POET: What about those Subgroups?**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Intravenous Treatment no. of events/total no. (%)</th>
<th>Oral Treatment no. of events/total no. (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>24/199 (12.1)</td>
<td>18/201 (9.0)</td>
<td>0.72 (0.37–1.36)</td>
<td>0.34</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤65.5 yr</td>
<td>9/83 (10.8)</td>
<td>7/91 (7.7)</td>
<td>0.68 (0.23–1.93)</td>
<td></td>
</tr>
<tr>
<td>&gt;65.5 yr</td>
<td>15/116 (12.9)</td>
<td>11/110 (10.0)</td>
<td>0.75 (0.32–1.70)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5/50 (10.0)</td>
<td>6/42 (14.3)</td>
<td>1.50 (0.42–5.59)</td>
<td>0.19</td>
</tr>
<tr>
<td>Male</td>
<td>19/149 (12.8)</td>
<td>12/159 (7.5)</td>
<td>0.56 (0.26–1.18)</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8/36 (22.2)</td>
<td>4/32 (12.5)</td>
<td>0.59 (0.12–1.78)</td>
<td>0.31</td>
</tr>
<tr>
<td>No</td>
<td>16/163 (9.8)</td>
<td>14/169 (8.3)</td>
<td>0.83 (0.39–1.76)</td>
<td></td>
</tr>
<tr>
<td>Renal disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5/25 (20.0)</td>
<td>5/21 (23.8)</td>
<td>1.35 (0.31–5.24)</td>
<td>0.40</td>
</tr>
<tr>
<td>No</td>
<td>19/174 (10.9)</td>
<td>13/180 (7.2)</td>
<td>0.64 (0.30–1.32)</td>
<td></td>
</tr>
<tr>
<td>Bacteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococci</td>
<td>10/104 (9.6)</td>
<td>8/92 (8.7)</td>
<td>0.90 (0.33–2.37)</td>
<td>0.50</td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
<td>7/46 (15.2)</td>
<td>4/51 (7.8)</td>
<td>0.47 (0.12–1.69)</td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>3/40 (7.5)</td>
<td>3/47 (6.4)</td>
<td>0.84 (0.15–4.78)</td>
<td></td>
</tr>
<tr>
<td>Coagulase-negative</td>
<td>4/10 (40.0)</td>
<td>3/13 (23.1)</td>
<td>0.45 (0.07–2.72)</td>
<td></td>
</tr>
<tr>
<td>Bacteria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6/75 (8.0)</td>
<td>3/77 (3.9)</td>
<td>0.54 (0.10–1.44)</td>
<td>0.50</td>
</tr>
<tr>
<td>No</td>
<td>18/124 (14.5)</td>
<td>15/124 (12.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of valve</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioprosthetic heart valve</td>
<td>11/53 (20.8)</td>
<td>6/56 (11.1)</td>
<td>0.48 (0.19–1.47)</td>
<td>0.35</td>
</tr>
<tr>
<td>Native heart valve</td>
<td>13/146 (8.9)</td>
<td>12/146 (8.2)</td>
<td>0.92 (0.40–2.09)</td>
<td></td>
</tr>
<tr>
<td>Involved valve</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic valve</td>
<td>16/109 (14.7)</td>
<td>11/109 (10.1)</td>
<td>0.65 (0.28–1.47)</td>
<td>0.56</td>
</tr>
<tr>
<td>Mitral valve</td>
<td>6/65 (9.2)</td>
<td>5/72 (6.9)</td>
<td>0.73 (0.20–2.56)</td>
<td></td>
</tr>
</tbody>
</table>

- Oral Treatment Better
- Intravenous Treatment Better
POET: Adverse Events

- Adverse effects: 6% (IV) vs. 5% (oral); \( p = 0.66 \)

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Intravenous Treatment n=12</th>
<th>Oral Treatment n=10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal, n(%)</td>
<td>0 (0%)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Renal Failure, n(%)</td>
<td>0 (0%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Hepatic Failure, n(%)</td>
<td>0 (0%)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Bone marrow suppression, n(%)</td>
<td>2 (17%)</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>Allergy, n(%)</td>
<td>10 (83%)</td>
<td>1 (10%)</td>
</tr>
</tbody>
</table>

?Courtesy of high dose amoxil and dicloxacilin

?Courtesy of linezolid
POET: Study’s Conclusion

“In patients with endocarditis on the side of the heart caused by streptococcus, *E. faecalis*, *S. aureus* or coagulase-negative staphylococci who were in clinically stable condition and who had an adequate response to initial treatment, a shift from initial intravenous to oral antibiotic treatment was noninferior to continued intravenous antibiotic treatment”
Questions or Comments?
Further Reading