Oral versus Intravenous Antibiotics for Bone and Joint Infection (OVIVA Trial)

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Background

- Standard of care for bone and joint infections involves weeks of intravenous (IV) therapy
  - Notion that oral (PO) antibiotics do not reach adequate bone concentrations
- Prior studies have already demonstrated success with treating bone and joint infections with PO antibiotics
  - Meta-analysis demonstrated no advantage of IV over PO therapy
  - Data from pediatric population shows efficacy of PO antibiotics for osteomyelitis

Cochrane Database Syst Rev 2013. :CD004439.
Clin. Infect. Dis. 2012. 54:393-407.

Clinical Question

In adult patients with bone or joint infection requiring at least 6-weeks of antibiotic therapy without sepsis or bacteremia, is treatment with PO antibiotics non-inferior to IV therapy for the first 6 weeks of therapy?

Question

Among the following patients, who should NOT be placed on oral antibiotics for the treatment of osteomyelitis:

A) Patient with implanted hardware at infection site

B) Patient with concomitant MRSA bacteremia

C) Patient with source control (debridement or surgery)

D) Patient with a high likelihood of medication compliance

MRSA = Methicillin-resistant *Staphylococcus aureus*

Design and Participants

- **Design**
  - Multi-center
  - Parallel group
  - Randomized
  - Open-label
  - Non-inferiority trial
- **Setting: 26 centers in the UK**
- **Enrollment: 2010-2015**
- **Follow-up: 1 year**
- **Analysis: Intention-to-treat**

Inclusion Criteria

- ≥18 years old
- Bone or joint infection requiring 6 weeks of antibiotics
  - Specific infections include one of the following:
    - Osteomyelitis of the extra-axial native skeleton
    - Native joint infection requiring excision arthroplasty
    - Prosthetic joint infection
    - Orthopedic fixation-device infection
    - Vertebral osteomyelitis +/- associated discitis or soft-tissue infection
- Received ≤7 days of IV therapy from date of definitive surgery or start of planned curative treatment if no surgery
- Life expectancy >1 year

Exclusion criteria

- *Staphylococcus aureus* bacteremia
- Any bacterial endocarditis on presentation or within prior month
- Mild osteomyelitis not requiring 6 weeks of therapy per judgement of clinician
- Septic Shock
- Infection where no oral option is a viable option
- Non-bacterial infection

Randomization and Interventions

- Within 7 days of definitive therapy, participants were randomized to a group:
  - **IV antibiotics** - Continued for 6 weeks
  - **PO antibiotics** - Continued for 6 weeks
    - 5 days of adjunctive IV therapy was allowed for the treatment of concurrent infections
- Investigator discretion
  - Adjunctive rifampin
  - Therapy beyond 6 weeks

Outcomes and Statistical Analysis

- Primary outcome
  - Definite treatment failure within 1 year after randomization
- Secondary outcome
  - Probable or possible treatment failure
  - Early discontinuation of therapy
  - Median hospital length of stay
  - Adverse events
- “worst case” outcome
  - PO therapy → assumes ALL participants with missing data **FAILED**
  - IV therapy → assumes ALL participants with missing data **SUCCEDED**

Baseline Characteristics

Characteristic	Intravenous Group (N= 527)	Oral Group (N= 527)	Total (N= 1054)
Age — yr			
Median (interquartile range)	61 (49–70)	60 (49–70)	60 (49–70)
Range	18–92	18–91	18–92
Male sex — no. (%)	320 (60.7)	358 (67.9)	678 (64.3)
Baseline surgical procedure — no. (%)			
No implant or device present; debridement of chronic osteomyelitis performed	153 (29.0)	169 (32.1)	322 (30.6)
No implant or device present; debridement of chronic osteomyelitis not performed	25 (4.7)	29 (5.5)	54 (5.1)
Debridement and implant retention	124 (23.5)	123 (23.3)	247 (23.4)
Removal of orthopedic device for infection	89 (16.9)	78 (14.8)	167 (15.8)
Prosthetic joint implant removed	68 (12.9)	67 (12.7)	135 (12.8)
Prosthetic joint implant, one-stage revision	47 (8.9)	43 (8.2)	90 (8.5)
Surgery for diskitis, spinal osteomyelitis, or epidural abscess; debridement performed	8 (1.5)	5 (0.9)	13 (1.2)

Baseline Characteristics (continued)

Deep-tissue histologic result — no. (%)			
Infected	266 (50.5)	277 (52.6)	543 (51.5)
Equivocal	13 (2.5)	17 (3.2)	30 (2.8)
Uninfected	31 (5.9)	32 (6.1)	63 (6.0)
Not done or missing†	217 (41.2)	201 (38.1)	418 (39.7)
Microbiologic diagnostic sampling — no. (%)			
Two or more samples positive for same organism	357 (67.7)	338 (64.1)	695 (65.9)
Two or more samples taken but only one positive for a given pathogenic organism	20 (3.8)	32 (6.1)	52 (4.9)
Only one sample taken, which was found to be positive for a pathogenic organism by closed biopsy	25 (4.7)	30 (5.7)	55 (5.2)
Two or more samples taken but only one positive for a given nonpathogenic organism	21 (4.0)	25 (4.7)	46 (4.4)
Sampling undertaken but no organisms identified	77 (14.6)	78 (14.8)	155 (14.7)
Not done or missing‡	27 (5.1)	24 (4.6)	51 (4.8)
Organisms identified — no./total no. (%)§			
Staphylococcus aureus	196/500 (39.2)	182/503 (36.2)	378/1003 (37.7)
Coagulase-negative staphylococcus	137/500 (27.4)	135/503 (26.8)	272/1003 (27.1)
Streptococcus species	72/500 (14.4)	73/503 (14.5)	145/1003 (14.5)
Pseudomonas species	28/500 (5.6)	23/503 (4.6)	51/1003 (5.1)
Other gram-negative organisms	84/500 (16.8)	84/503 (16.7)	168/1003 (16.7)
Culture negative	77/500 (15.4)	78/503 (15.5)	155/1003 (15.5)

Antibiotic Therapy

Table S10: Overview of actual antibiotics (excluding rifampicin), as defined by agents used for more than one week during the initial six-week treatment period

	Participants randomized to IV Antibiotic* (N = 521)	Participants randomized to PO Antibiotic* (N = 523)	Total* (N = 1044)
Glycopeptides[a] (IV)	214 (41.1%)	**22 (4.2%)**	236 (22.6%)
Penicillins (IV)	38 (7.3%)	11 (2.1%)	49 (4.7%)
Cephalosporins (IV)	173 (33.2%)	**8 (1.5%)**	181 (17.3%)
Carbapenems (IV)	41 (7.9%)	5 (1.0%)	46 (4.4%)
Other single IV antibiotic	35 (6.7%)	2 (0.4%)	37 (3.5%)
Combination IV antibiotics	35 (6.7%)	6 (1.1%)	41 (3.9%)
Penicillins (PO)	8 (1.5%)	83 (15.9%)	91 (8.7%)
Quinolones[b] (PO)	**33 (6.3%)**	191 (36.5%)	224 (21.5%)
Tetracyclines[c] (PO)	**4 (0.8%)**	57 (10.9%)	61 (5.8%)
Macrolides / Lincosamide [d] (PO)	**10 (1.9%)**	68 (13.0%)	78 (7.5%)
Other single PO antibiotic (PO)	10 (1.9%)	54 (10.3%)	64 (6.1%)
Combination PO antibiotics (PO)	13 (2.5%)	87 (16.6%)	**100 (9.6%)**

Outcomes: Primary

Definite treatment failure within 1 year after randomization:

13.2% (67/509) PO vs. 14.6% (74/506) IV

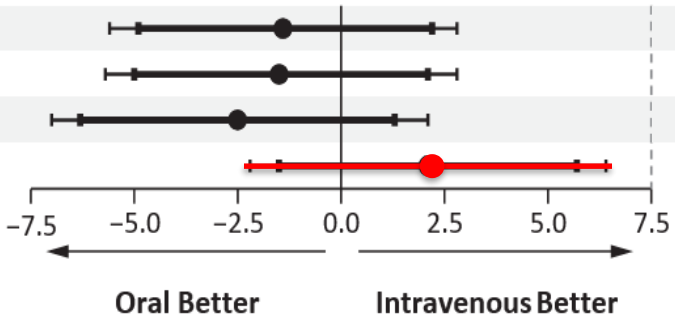
(risk difference oral vs. IV -1.4%; 95% CI -5.6 to 2.9)*

* Missing data were imputed

Results by study population

Figure 3. Differences in Risk According to the Analysis Performed.

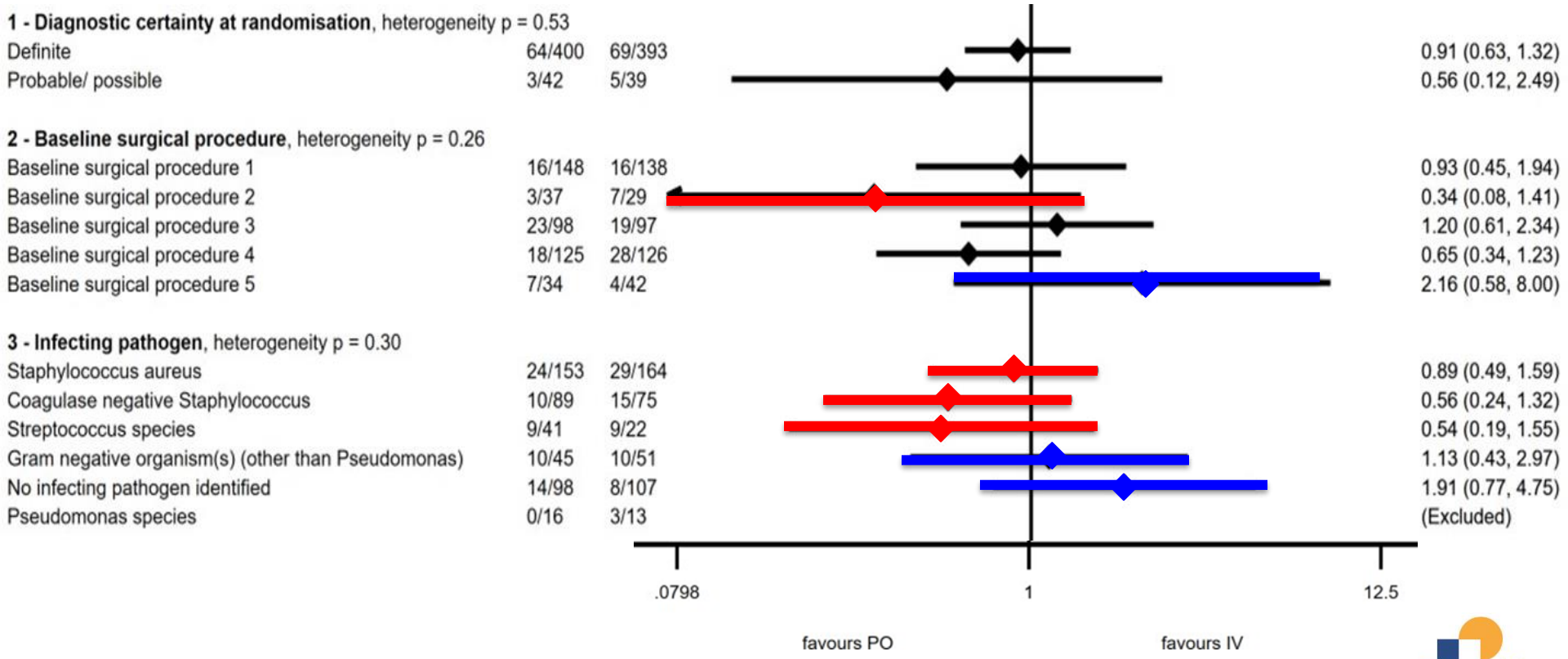
Subgroup	Oral Group	Intravenous Group	Risk Difference (90% CI; 95% CI)
	patients with treatment failure/ total no. of participants		
Intention-to-treat population	70.0/527	77.3/527	−1.4 (−4.9 to 2.2; −5.6 to 2.9)
Modified intention-to-treat population	67/509	74/506	−1.5 (−5.0 to 2.1; −5.7 to 2.8)
Per-protocol population	61/466	69/443	−2.5 (−6.3 to 1.3; −7.0 to 2.1)
Worst-case sensitivity analysis	85/527	74/527	2.1 (−1.5 to 5.7; −2.2 to 6.4)



Outcomes: Secondary

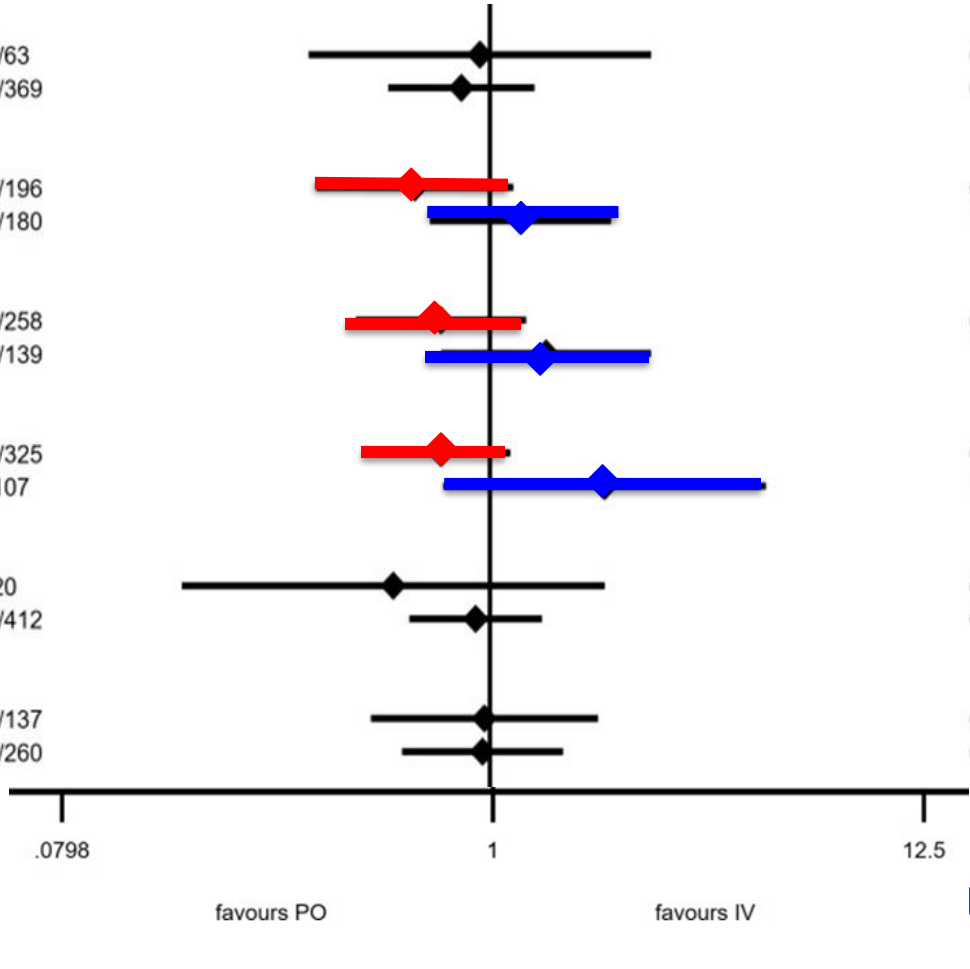
- **Probable or possible treatment failure**
  - 2.0% (10/506) PO vs. 1.2% (6/506) IV
- **Early discontinuation of therapy**
  - 12.8 (67/523) PO vs. 18.9% (99/523) IV
    - P = 0.006
    - ARR 6.1
    - NNT 16
- **Median hospital length of stay**
  - 11 days PO vs. 14 days IV, P < 0.001

Subgroup analysis



Subgroup analysis

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)
6 - Metal retained, heterogeneity p = 0.13			
No metal retained	34/269	43/258	0.76 (0.47, 1.23)
Metal retained	30/132	23/139	1.37 (0.76, 2.49)
7 - Infecting pathogen (known vs. unknown), heterogeneity p = 0.07			
Any known infecting pathogen	53/344	66/325	0.76 (0.51, 1.12)
No infecting pathogen identified	14/98	8/107	1.91 (0.77, 4.75)
8 - Peripheral vascular disease, heterogeneity p = 0.47			
Yes	3/23	9/20	0.58 (0.18, 1.91)
No	61/419	65/412	0.92 (0.63, 1.34)
9 - Antibiotic cement/ beads used, heterogeneity p = 0.98			
Yes	22/148	21/137	0.97 (0.51, 1.84)
No	42/253	45/260	0.96 (0.61, 1.51)



Adherence

Table S6: Self-reported adherence with antibiotics at day 14 & 42 using the Morisky Adherence Measure [8] *(Maximum score is 8)*

	IV Antibiotic (N = 72†)	PO Antibiotic (N = 303)	Total (N = 375)
Adherence score* (Day 14)	8 (8, 8), (5, 8)	8 (7, 8), (1, 8)	8 (8, 8), (1, 8)
Adherence categories[a] (Day 14)			
High adherence	49 (68.1%)	207 (68.3%)	256 (68.3%)
Medium adherence	20 (27.8%)	71 (23.4%)	91 (24.3%)
Low adherence	2 (2.8%)	18 (5.9%)	20 (5.3%)
Missing[b]	1 (1.4%)	7 (2.3%)	8 (2.1%)
	IV Antibiotic (N = 80)	**PO Antibiotic (N = 323)**	**Total (N = 403)**
Adherence score* (Day 42)	8 (7, 8), (4, 8)	8 (7, 8), (0, 8)	8 (7, 8), (0, 8)
Adherence categories[a] (Day 42)			
High adherence	54 (67.5%)	166 (51.4%)	220 (54.6%)
Medium adherence	21 (26.3%)	117 (36.2%)	138 (34.2%)
Low adherence	3 (3.6%)	25 (7.7%)	28 (7.0%)
Missing[b]	2 (2.5%)	15 (4.6%)	17 (4.2%)

Adverse Events

- **Complications from the IV catheter**
  - 1.0% (5/523) PO vs. 9.4% (49/523) IV
    - P< 0.001, ARR 8.4%, NNT 12
- **C. Diff diarrhea**
  - 1.0% (5/523) PO vs. 1.7%(9/523)
    - P = 0.30
- **At least one serious adverse event**
  - 26.2% (138/527) PO vs. 27.7% (146/527)
    - P = 0.58

Limitations

- Incidence of serious adverse events was unexpectedly very high compared to similar studies
- Open-label design
- High rates of medication adherence or follow-up reported in the study may not be reflective of actual rates
- Specific antibiotic regimens and doses were not reported
- No direct comparison of antimicrobial agents assessed

Clinical Application

- *Oral antibiotic therapy is noninferior to intravenous therapy for bone/joint infections treated for 6 weeks*
  - Provides an alternative for patients who are not candidates or refuse prolonged IV therapy
- Included large number of patients without histologic data and/or negative cultures
- *C. diff* rates did not differ between groups

Question

Among the following patients, who should NOT be placed on oral antibiotics for the treatment of osteomyelitis:

A) Patient with implanted hardware at infection site

B) Patient with concomitant MRSA bacteremia

C) Patient with source control (debridement or surgery)

D) Patient with a high likelihood of medication compliance

MRSA = Methicillin-resistant *Staphylococcus aureus*

References

- Li HK, Rombach I, Zambellas R, Walker AS, McNally MA, Atkins BL, et al. (2019). Oral versus Intravenous Antibiotics for Bone and Joint Infection. New England Journal of Medicine, 380(5), 425–436. doi:10.1056/nejmoa1710926.
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