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Osteomyelitis and infected non-unions: can we talk about over-treatment?

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What we currently know

Chronic osteomyelitis is a long-standing bone infection, notoriously difficult to cure; high risk of relapse

It involves necrotic bone (sequestra) and biofilm formation

Exposed fractures are at high risk of chronic osteomyelitis→ infected non-unions

Requirement of an effective and safe treatment

Treatment historically involves:

a) Surgical debridement/resection (effective source control)

b) Antibiotic therapy

Myth of long-course, parental antibiotic therapy for chronic osteomyelitis: where from?

- **Waldvogel et al. - NEJM 1970:**

"In our experience, osteomyelitis is rarely controlled without the combination of careful, complete surgical debridement and prolonged (4 to 6 wks) parenteral antibiotic therapy at high dosage"

Limitations

1. Retrospective study on 247 pts
2. Heterogeneous patients
3. Poorly effective oral antibiotics

But ... what does the literature say today?

Breaking of two paradigms regarding chronic osteomyelitis

A

Antibiotic therapy by definition administered at high-dose and intravenously

B

Long duration of antibiotic therapy regardless of concomitant surgical strategy

Unnecessarily prolonged antimicrobial treatment → antibiotic resistance & toxicity/adverse effects

Systemic Antibiotic Therapy for Chronic Osteomyelitis in Adults

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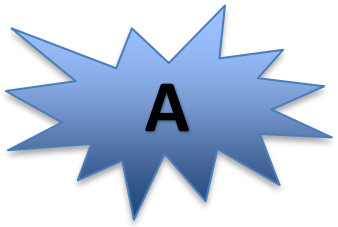


Clinical Infectious Diseases, 2011

Effectiveness of oral treatment

Parenteral therapy achieves cure rates of **60–90%, but**

- **Oral antibiotics** with high bioavailability → **therapeutic bone levels**; **comparable cure rates** (up to 98% with aggressive regimens + debridement)
- Rational choice of oral drugs with **appropriate PK/PD profile** (preferring antibiotics with high bone diffusion (ratio bone-blood >0.3) and good oral bioavailability (>90%), particularly if concomitant surgical debridement

Antibiotic	Oral Bioavailability (%)	Bone/Blood Concentration Ratio	Notes
Ciprofloxacin	70–80	0.3–0.5	Effective against Gram-negatives; good bone penetration
Levofloxacin	~99	0.4–0.6	Broad-spectrum; excellent bioavailability
Clindamycin	~90	0.4–0.7	Good activity against anaerobes; effective in bone infections
Rifampin	~90	0.2–0.3	Active against biofilm; always used in combination therapy
Trimethoprim-Sulfamethoxazole	85–90	0.4–0.6	Good bone penetration; useful in Staphylococcus aureus infections
Linezolid	~100	~0.4 or higher	Active against resistant Gram-positives; excellent oral bioavailability
Tetracyclines (Doxycycline, Minocycline)	80–90	0.6–0.8	Broad-spectrum; good bone penetration
Metronidazole	90–100	0.75–1.0	Active against anaerobes; excellent bone diffusion

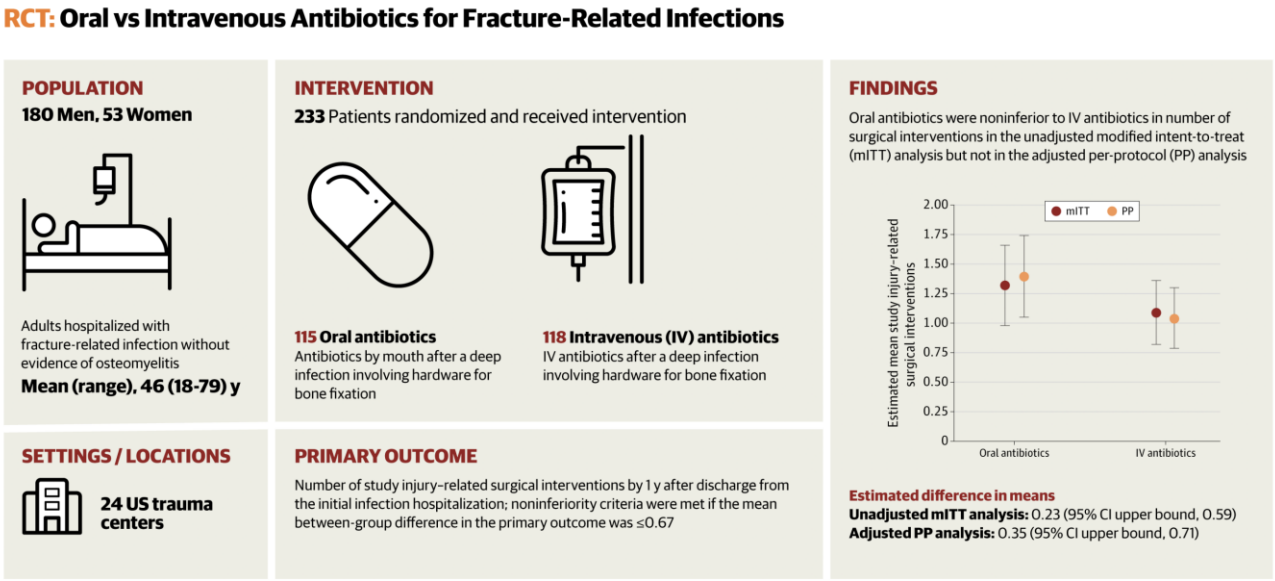
Success = absence of osteomyelitis signs at long term follow up (most studies >1 year)

Recent literature evidence

- **OVIVA trial (Li et al., 2019):** non-inferiority of oral regimen during 6 weeks for BJI (after 1 week of IV) compared to IV regimen [1.054 adults with BJI (osteomyelitis, PJI, hardware)]; 527 oral vs 527 IV. Primary outcome: treatment failure at 1 year: IV 14.6%, oral 13.2%, difference: –1.4% (95% CI: –5.6 to +2.9)

- **Oral Is the New IV, a Systematic Review (Walk-Dickler et al., 2022):** 21 prospective trials comparing oral vs IV. Osteomyelitis: 8 RCTs, n=1.321; no RCT showed IV superiority → treatment success (oral vs IV) 84% vs 83%

- **POvIV RCT:** efficacy of oral vs IV tp for FRI (exclude osteomyelitis) → non-inferiority in preventing further surgeries over a 1-year period in mITT



Oral therapy advantages

- Good evidence on literature (> 40 observational studies, 10 RCTs) → success rates consistently similar for both routes
- Lower discomfort for the patient
- Avoiding risks of central venous access
- Lower costs
- Reducing length of hospital stay

Prolonged parenteral antibiotic therapy has not been shown to be associated with non-recurrence → **oral antibiotic therapy is fully justified**

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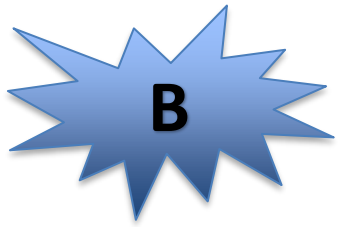


Clinical Infectious Diseases, 2011

Optimal Duration of Therapy

- No strong evidence supports durations longer than **6 weeks for chronic non-vertebral osteomyelitis**

- **Surgical debridement** increases success rates and may reduce antimicrobial therapy duration

- Over-treatment: risk of antimicrobial resistance and toxicity

Cure is achievable with antibiotics alone in selected cases (e.g., no hardware retention, localized disease)

Remission = complete clinical resolution of previous infection after a two-year follow-up

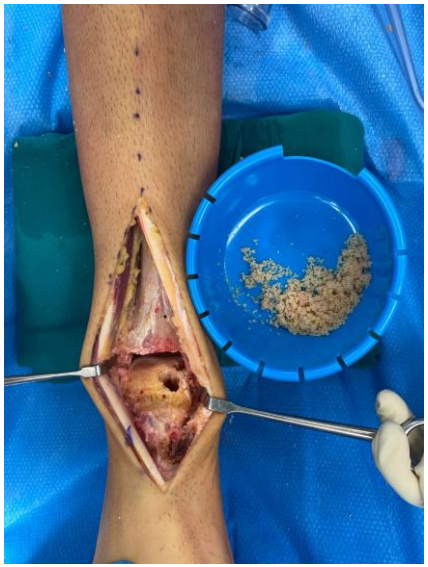
Recent literature evidence

- **Duration of post-surgical antibiotic therapy for adult chronic osteomyelitis: a single-centre experience (Rod-Fleury et al., 2011):** observational study; short (6 weeks) vs. long (12 weeks) antibiotic therapy after surgery

  [debridement and lavage, insertion of antibiotic beads, intramedullar reaming, use of vacuum-assisted devices, external fixation]

- ❖ No significant difference in treatment failure (recurrence, persistence, re-operation) between short and long courses: OR = 1.02, 95% CI [0.45–2.29]
- ❖ Short-duration therapy showed similar efficacy when adequate debridement was performed
- ❖ Short therapy reduces side effects, antimicrobial resistance, and cost
- ❖ Early switch to oral antibiotics with good bioavailability
- ❖ Limited sample size: n = 83 patients.

More RCTs are needed.



Conclusions

- **Oral short-course antibiotic** therapy for chronic osteomyelitis is supported by strong evidence
- Source control (surgical debridement/resection) can reduce antimicrobial therapy duration
- Need for personalization and case-by-case evaluation
- Evolving guidelines: possible transition to early oral therapy
- Importance of multidisciplinary management