Antibiotics For Osteomyelitis: *Boneheaded or Brilliant?*

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Challenging the “Standard”
- Traditional thinking states:
  The “Standard of Care” for antibiotic therapy in osteomyelitis is 4-6 weeks of IV therapy following the *definitive debridement*
- Is this really the case??

Design a Trial for Osteomyelitis
- How do you diagnose osteomyelitis
  - Bone Biopsy
  - Culture
  - Pathology
  - Imaging
  - PTB
- How long do you treat?
- What route of antibiotic therapy?
- What is the role of surgery?
- *How do you define a cure?*

What do you do in a case such as this?
Now let’s say that the patient refuses surgery
What about this case? Osteo or Charcot & what do we do about it?

This patient DOES refuse surgery!

Empirical Basis

Antibiotic therapy alone has worked for every one of us at one time or another!

There are just some situations where you can not do surgery or give 6 weeks IV

BASELINE - ENTEROBACTER OSTEO DISTAL PHALANX

Courtesy: R. Daryl Phillips, DPM
WEEK 7 - ENTEROBACTER OSTEO DISTAL PHALANX

MUST READ Reference
Brad Spellberg & Ben Lipsky: Systemic antibiotic therapy for chronic osteomyelitis in adults
Clinical Infectious Diseases, Feb 1, 2012

IWGDF Diabetic Foot Osteomyelitis Systematic Review Findings:
- 1168 papers identified, only 19 met criteria (only 3 were controlled clinical trials)
- No significant differences in outcome were associated with any particular treatment strategy
- There was no evidence that surgical debridement of the infected bone is routinely necessary
- There was no data to support the superiority of any particular route of delivery of systemic antibiotics or to inform the optimal duration of antibiotic therapy
- No available evidence supports the use of any adjunctive therapies, such as hyperbaric oxygen, granulocyte-colony stimulating factor or larvae

Cochrane Review – Sept 2013
- The pooled results did not show any difference between people given antibiotics by mouth or parenterally.
- The way antibiotics are given does not impact on the disease remission rate if the bacteria causing the infection are sensitive to the antibiotic used.
- There was either no or insufficient evidence on which to base judgements about the optimum length of antibiotic treatment or the best antibiotics to use
www.cochrane.org

Deep Sinus Tract Cultures
Bernard, et al, Int. JID 2009
- Non randomized, prospective study
- 147 pts 154 episodes of osteo
- 4 samples
  - Two consecutive sinus tract cx w/ bone contact at different times – “A”
  - Surgical biopsy through sinus tract – “B”
  - Surgical biopsy through non infected site (“gold standard”) – “C”

Results
- When both sinus tract cultures yielded the same organism:
  - concordance between A&C = 96%
  - Sensitivity = 91%
  - Specificity = 86%
  - Accuracy = 90%
- NO difference if antibiotics were stopped or not
Senneville *Diabetes Care* 2008

- 50 consecutive patients treated non-surgically
- Mean duration of therapy was 11.5 ± 4.21 weeks
- At the end of a 12.8 month post-treatment mean follow-up, 32 patients (64%) were in remission.
- Bone-culture-based antibiotic therapy was the only variable associated with remission, as determined by both univariate and multivariate analysis (OR 4.78, 95% CI 1.0-22.7, P=0.04).
- **Conclusions:** Bone-culture-based antibiotic therapy is a factor predictive of success in diabetic patients treated non-surgically for osteomyelitis of the foot.

“Conservative” Treatment

- Defined as predominantly abx with little or no surgical debridement
- Number of reported pts now >500
- Satisfactory response was observed in the majority
  - *Jeffcoate & Lipsky CID* 2004

When the 2012 IDSA Guidelines Suggest *Medical Therapy*

<table>
<thead>
<tr>
<th>Table 10: Approach to Treating a Patient With Diabetic Foot Osteomyelitis</th>
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<tbody>
<tr>
<td>When to consider a trial of nonsurgical treatment</td>
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<tr>
<td>- No persisting sepsis after 48-72 h if on treatment</td>
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<td>- Patient can receive and tolerate appropriate antibiotic therapy</td>
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<td>- Degree of bony destruction has not caused irretrievable compromise to mechanics of foot bearing in mind potential for bony reconstitution</td>
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<td>- Patient prefers to avoid surgery</td>
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<td>- Patient comorbidities confer high risk to surgery</td>
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<td>- No contraindications to prolonged antibiotic therapy (eg, high risk for <em>C. difficile</em> infection)</td>
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<td>- Surgery not otherwise required to deal with adjacent soft tissue infection or necrosis</td>
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When the 2012 IDSA Guidelines Suggest *Surgical Therapy*

<table>
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<th>When to consider bone resection</th>
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<tr>
<td>- Persistent sepsis syndrome with no other explanation</td>
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<tr>
<td>- Inability to deliver or patient to tolerate appropriate antibiotic therapy</td>
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<tr>
<td>- Progressive bony deterioration despite appropriate therapy</td>
</tr>
<tr>
<td>- Degree of bony destruction irretrievably compromises mechanics of foot</td>
</tr>
<tr>
<td>- Patient prefers to avoid prolonged antibiotics or to hasten wound healing</td>
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<tr>
<td>- To achieve a manageable soft tissue wound or primary closure</td>
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<tr>
<td>- Prolonged antibiotic therapy is relatively contraindicated or is not likely to be effective (eg, presence of renal failure)</td>
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Non-Surgical Studies

  - 17/22 (77%) diabetics with osteo resolved completely with oral antibiotics only (up to 6 years follow up)
- *Pillert, Arch Intern Med* 1999
  - 50 pts, occasional debridement, 100% IV
  - 70% remission rate
- *Yadlapalli, Wounds* 2002
  - 58 pts, 100% IV
  - 79% remission rate

Non-Surgical Studies

- *Embil, Diabetic Foot 2000 (DFCON 2005)*
  - 128 pts
  - All (or mostly) oral therapy
  - 80% remission
  - >1 yr f/u relapse free
- *Ha Van, Diabetes Care* 1996
  - 57% cure antibiotics alone
  - 78% cure antibiotics + “conservative” surgery
Non-Surgical Studies

- **Embil, Foot & Ankle Int., Oct 2006**
  - 79 pts, 93 episodes of osteomyelitis
  - Mean of 1.6 pathogens from culture
  - 3 +/- 1 oral agent (with/without initial short IV)
  - Bone debridement in 26 (28%) toe amp in 9
  - Mean duration of oral therapy = 40 +/- 30 wks
  - 75 (80.5%) put into remission

  **Conclusion:** DF osteo was effectively managed with oral abx with or without limited office debridement

Primarily Non-Surgical Management of Osteomyelitis of the Foot in Diabetes

- 147 pts/5 yr period
- 113 non-surgical, 34 surgical
- 18% admitted for IV, rest treated with orals
- Mean length of oral treatment 61 days (max>300)
- "The results confirm that although urgent surgery is indicated in some patients, non-surgical management of those without limb-threatening infection is associated with a high rate of apparent remission."

Flowchart from Game & Jeffcoate Study

- No surgery required n = 113
  - Recurrence n = 35 (31%)
    - Surgery n = 8
  - Antibiotics alone n = 27
  - Remission without further treatment n = 66 (58.4%)
  - Remission without surgery N = 93 (82.3%)

- Surgery required n = 34
  - Recurrence n = 17 (60.7%)
    - Surgery n = 10
  - Antibiotics alone n = 7
  - Remission w/ minor amputation N = 22 (78.6%)

"Conservative" Management of DFO

- Retrospective, consecutive pts between 2003-2008 at a clinic in the UK
- 130 patients initially treated with oral antibiotics
  - 66.9% healed with abx alone
  - 13.9% required amputation
  - MRSA associated with adverse outcome
- Multiple problems with definitions/design

Antibiotics vs. "Conservative" Surgery

- Prospective, randomized comparative trial
- Two groups
  - AG = antibiotics alone for 90 days
  - SG = conservative surgery + 10 days abx
- Followed for 12 weeks after healing
- Results
  - 18 (75%) healed in AG group
  - 19 (86.3%) healed in SG group (p = 0.33)

  **Lazarro-Martínez et al., Diabetes Care, Oct 15 2013**

Criticalisms of Lázaro-Martínez DFO RCT

- Excluded pts with severe infxn, PAD, poor glycemic control; only 1/3 of evaluated pts enrolled
- No diagnostic bone culture in antibiotic only group
- "Surgical" pts had abx ≤ 2 wks pre- & 10 d post-randomization
- 1° outcome was "healing" of ulceroperative wound
- All sites eligible but only forefoot cases enrolled
- More metatarsal head & hallux ulcers in surgical group; more toe ulcers antibiotic group
- Possible effect on outcomes if IV or shorter than Rx 90 course of abx, or more aggressive surgical debridement
- Possibly inadequate antibiotic Rx (amox/clav po tid)
- Evaluation was not done on ITT population

  **Lipsky BA. Diabetes Care 2014;37:599**
  **Landman et al, Diabetes Care 2014;37:789**
DFO treated initially with nonsurgical management

- Retrospective study of 100 consecutive patients initially treated nonsurgically – 85 met criteria and analyzed
- Remission defined as wound healing with no clinical or radio signs of osteo at 12 mo
- Results
  - 54 (63.5%) remission with nonsurgical alone
  - 29 (34.5%) had an amputation
  - 14 (26%) admitted for IV abx


IWGDF Antibiotic Consensus

- No specific agent has been shown to be most effective
- Empiric coverage should include anti-staph (including MRSA?)
- No data indicates superiority of any particular route of administration
- No data to inform duration of therapy
  - IDSA Guidelines “appears useful”

www.iwgdf.org

Duration of Therapy

No residual infected tissue (eg, postamputation)
- Parenteral or oral...
- 2-5 d
No residual infected soft tissue but not bone
- Parenteral or oral...
- 1-3 wk.
No residual infected but viable bone
- Initial parenteral, then consider oral switch...
- 4-6 wk
No surgery, or residual debrid bone postoperatively
- Initial parenteral, then consider oral switch...
- >3 mo

IDSA Diabetic Foot Guidelines, CID, June 2012

Conclusions

“This accumulated evidence suggests it is time to revisit the traditional belief in the need for routine surgical intervention”

Jeffcoate & Lipsky CID 2004

Conclusions Spellberg & Lipsky

- Oral antibiotic therapy with highly bioavailable agents is an acceptable alternative to parenteral therapy
- Adding rifampin to a variety of antibiotic regimens improves cure rates
- Individualize duration of therapy based on patient’s clinical and radiographic response
  - No strong evidence supports 4-6 weeks of therapy after surgical debridement
- Surgical resection appears to increase cure rates. However, not all cases of chronic osteo require it