# Meta-Analysis: Outcomes of Surgical Vs Medical Management of Diabetic Foot Osteomyelitis

David H Truong, DPM, MS[1,2], Matthew Malone, Ph.D[3,4], Dane K. Wukich, MD[2], Javier LaFontaine, DPM, MS[2,5], Lawrence A. Lavery, DPM, MPH[2,5]

[1]Surgical Service – Podiatry, VA North Texas Health Care System, Dallas, Texas, USA; [2]Department of Orthopaedic Surgery, University of Texas Southwestern Medical Center, Dallas, Texas, USA; [3]Infectious Disease & Microbiology, School of Medicine, Western Sydney University, Campbelltown, Australia; [4]South West Sydney Limb Preservation and Wound Research Academic Unit, South Western Sydney LHD, Sydney, Australia; [5]Department of Plastic Surgery, University of Texas Southwestern Medical Center, Dallas, Texas, USA

## INTRODUCTION

Current treatments for diabetic foot osteomyelitis (DFO) are often poorly supported by clinical evidence; study sizes are typically small and the operational definitions to define DFO and its outcomes are inconsistent. Many of the recommendations made by the Infectious Disease Society of America (IDSA) and International Working Group on Diabetic Foot (IWGDF) are based on low levels of graded evidence. Historically, surgeons believed that to cure osteomyelitis a surgical approach was needed to excise or amputate the nidus of infection. Other physicians have favored a conservative non-surgical (i.e. medical management) approach of the pathology. Unfortunately, there is relatively little evidence to help guide clinicians as to the optimal antibiotic agent/s, dosing, or their most effective duration of regimens.

Most of the existing literatures are from small retrospective studies with few prospective studies. Recommendations are often biased based on the background of the specialists that developed the criteria. The aim of this meta-analysis is to evaluate the quality of the evidence for the treatment (Surgical versus Medical Management) of DFO and to compare the clinical outcomes of each.

## METHOD

*Definition of medical management*

Treatment of infected bone that does not involve surgical resection or amputation of the bone. Patients may undergo incision and drainage, bone biopsy, and other soft tissue procedures.

*Definition of surgical management*

Treatment that involved surgical resection or amputation of the infected bone(s).

*Search strategy*

A PubMed search was performed using the input "conservative, osteomyelitis, foot" as keywords for medical treatment of OM until January 2020. A repeat search with the keywords "surgical, osteomyelitis, foot" were used for surgical treatment of OM. All articles were reviewed by 2 authors (DHT and LAL). We included articles that were related to diabetic foot OM. We excluded articles that involved Charcot Arthropathy, case reports, small case series, review articles, commentaries, non-human studies, and articles that were not in English.

*Outcomes of interest*

Each article was reviewed for: the study design, antibiotic duration, number of subjects with DFO, criteria for DFO, follow up duration of DFO, defined criteria for treatment success, adverse events, percentage of treatment success, peripheral perfusion or the presence of peripheral arterial disease, peripheral neuropathy, and hemoglobin A1c (Tables 1 and 2).

*Statistics*

A pooled weighted analysis ($\chi^2$) was performed of the data using the Meta-Essentials Excel package program. All data were combined, and a weighted effect of the results was created in addition to determining the weight of each individual study using an inverse variance method with random effect model. The effect and odds ratios were measured for each group. The effect size was represented on a Forest Plot with 95% confidence interval. $I^2$ was used to determine the magnitude of heterogeneity whereas Cochran Q and $P_Q$ were used to determine the presence of heterogeneity. Furthermore, $\tau^2$ and $\tau$ were calculated, where $\tau^2$ reflects the variance of the true effect size. Both $\tau^2$ and $\tau$ represent the true heterogeneity.

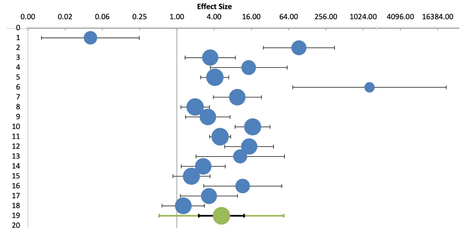



**Fig 2:** Forest Plot of Medical management of OM

| # | Reference | Study | N | Duration of Antibiotic | Follow-up (months) | OM Reference Standard | Tx Success Reference Standard | Success Rate | QUADAS-2 Bias Risk |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Mauler 2017 | Retrospective | 18 | 2-14 days IV followed by 4 weeks to 9 months PO | NR | MRI, CT, or XR with deep ulcer and PTB | NR | 17% | Low |
| 2 | Lesens 2015* | Retrospective | 39 | 11 ± 1 weeks | 21 ± 1 | Bone Culture | 1) complete healing of wound,<br>2) no SOI 6 months after completion of antibiotic therapy, and<br>3) a stable or improved bone on XR | 87% | Low |
| 3 | Tone 2015 | Prospective RCT | 40 | 50% 6 weeks<br>50% 12 weeks | 12 | XR and Bone culture after at least 2 weeks of antibiotic-free period | complete and persistent (> 4 weeks) of:<br>1) healing of wound<br>2) absence of recurrent infection<br>3) no need for bone resection or amputation at 1 year | 65% | High |
| 4 | Lazro-Martinez 2014* | Prospective RCT | 24 | 90 days | 12 | PTB and XR changes | Complete epithelialization | 79% | High |
| 5 | Acharya 2013 | Retrospective | 130 | NR | NR | Chronic ulcer >4 weeks PTB, visible bone, or sausage toe | NR | 66.9% | High |
| 6 | Mutluoglu 2013 | Retrospective | 37 | 16 – 66.6 days | 12 | bone cx (n=17), MRI if bone cx is not available (n=20) | 12 months period free of wound recurrence | 97.3% | Low |
| 7 | Valabhji 2009 | Retrospective | 53 | 6 months average (3-12)<br><br>If no improvement on MRI, then antibiotic was continued for another 3 months | 15 | MRI | MRI demonstrate resolution or improvement in OM signal changes | 75% | Low |
| 8 | Jeffcoate 2008 | Retrospective | 113 | PO = 61 days (3-349 days)<br>IV median length = 16 days (1-44 days) | 12 | Clinically based and XR changes<br><br>MRI and WBC-Bone scan when patient has Charcot or author continue uncertainty | Patient survived with limb intact at 12 months after the point at which the doctor felt the infection had been eradicated | 58% | High |
| 9 | Senneville 2008 | Retrospective | 50 | 11.5 ± 4.21 weeks | 12 | At least 2 of the following:<br>1) Wound > 2 weeks over a bony prominence with an ulcer > 2cm sq or depth > 3mm, assoc. w/ PTB and/or<br>2) changes consistent w/ OM on XR, bone scan, or MRI | Absence of any SOI at the initial or contiguous site assessed at least 1 year after the end of treatment | 64% | High |
| 10 | Embil 2006 | Retrospective | 117 | PO 40 ± 30 weeks | NR | Ulcer w/ drainage w/ one or more of:<br>1) (+) Xray change<br>2) (+) bone scan<br>3) visible or PTB<br>4) (+) culture | NR | 80.5% | High |
| 11 | Tice 2003 | Retrospective | 236 | 13-43 days | 6 | XR, wound culture with PTB or aspiration | No infection manifesting at the same site.<br>If microbiology report was available, recurrence was classified as either "relapse" (original pathogen), or "reinfection" (different pathogen) | 69% | Low |
| 12 | Yadlapalli 2002 | Retrospective | 58 | 81% IV antibiotic 4-6 weeks<br><br>19% 19-90 days culture specific antibiotic regime | 12 | Clinically appear infected, exposed bone, Xray changes, or positive bone scan | Complete ulcer healing at 12 months | 79.3% | High |
| 13 | Senneville 2001 | Retrospective | 17 | 6 months | 22 | Bone scan and Biopsy | Disappearance of all SOI at the end of treatment and absence of relapse during follow up | 76.5% | High |
| 14 | Pittet 1999 | Retrospective | 50 | 24 ± 18 days of IV followed by at least 6 weeks of PO antibiotics | 25 ± 15 months | clinical infection with XR changes and positive bone scan. | Ulcer healed completely with no sign of relapse at the same site or contiguous site after at least 5 months | 61% | Low |
| 15 | Ha Van 1996* | Retrospective | 67 | 246.9 ± 232 days | NR | NR | Complete epithelization | 56.7% | High |
| 16 | Venkatesan 1997 | Retrospective | 22 | 12 Weeks | 27 | XR with unequivocal clinical and radiological evidence of bone infection | Inferred from freedom from clinical SOI and evidence of radiologic healing | 77% | High |
| 17 | Peterson 1989 | Prospective | 31 | 3 months | 12 | XR or Bone scan | Did not require re-hospitalization for repeat antibiotic or amputation | 65% | High |
| 18 | Bamberger 1987 | Retrospective | 51 | 4 week IV to 10 weeks with IV + PO | 19 | Required all 3:<br>1) XR changes<br>2) clinical sign of inflammation<br>3) (+) wound, bone, or blood culture | Clinical resolution at time of last follow up visit w/o need for amputation | 52.9% | High |

**Table 1:** Studies for medical management. XR = x-ray (plain); PTB = probe-to-bone; MRI = magnetic resonance imaging; CT = computerized tomography; SOI = sign of infection; NR = not reported; SOI = sign of infection; IV = intravenous; PO = by mouth

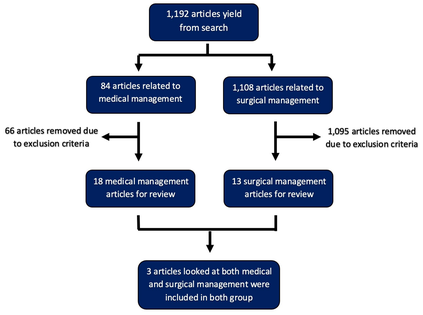



**Fig 1:** Result of search analysis. 31 articles qualified for review at the end after exclusion criteria were applied.

## META-ANALYSIS

The Q value for medical management of DFO was 125.58 and for surgical management it was 130.20, both with a *p*-value of 0.00, indicating that heterogeneity existed in the study. The $I^2$ value for the medical management of DFO was 86.46%, whereas for surgical management, it was 90.78%. The high percentage indicated that the population studied were not the same. Since $I^2$ values were high, publication bias could not accurately be calculated. τ was used to evaluate the dispersion of true effect sizes. $\tau^2$ and τ for medical and surgical management were as follows: 1.04, 1.02 and 0.97 and 0.98, respectively.

The forest plots (Fig. 2 and 3) depict the representation of the confidence intervals (CI), effect size, and study weight of all the studies for the medical and surgical management of DFO, respectively. The numerical data of the graphs and the odds ratios are displayed in Tables 3 and 4. The vertical line in Figure 2 represented no effect and the study was considered to have no significant findings when its CI crossed.

In Figure 2, only one study (Mauler et al.) was on the left of the vertical line, and this indicated there was a negative correlation between medical treatment and outcomes. Two studies (Ha Van and Bamberger) CI's crossed the vertical line, suggesting that their findings were not significant. The studies on the right side of the vertical line show a positive correlation between successful management of osteomyelitis with medical management. The overall combined weight of the studies (line 19, Fig. 2) CI did not cross the vertical line; and thus, indicated that the overall finding was significant. However, because if the high $I^2$ value, we cannot rely on the combined CI, but rather the prediction interval (PI) instead, which gave us the range of where the estimated 95% of future studies will fall. The PI range was 0.52-53.08, and it did cross the vertical line as well, indicating that the future studies finding may not be significant and that the outcome may not be favorable.

In Figure 3, all the studies were on the right side of the vertical line, which is represented by effect size 1.00. Thus, all surgical management of osteomyelitis resulted in a positive correlation. Moreover, since none of the studies' CI crossed the vertical line, all the studies were considered to have significant findings as well. Again, due to the high $I^2$ value, we cannot rely on the CI in this case as well. The combined weight of all the study yielded a PI (3.68-460.94) that was on the right side of the vertical line and did not cross it, indicating that future studies of surgical management will yield positive results as well.

## DISCUSSION

This meta-analysis highlights several important limitations in DFO study designs:

- The gold standard to diagnose osteomyelitis is bone culture and histology, but this is often not use and it is almost never used to define treatment success or failure.
- Most studies used different criteria to define DFO, treatment success, PAD, and peripheral neuropathy.
- Most studies criteria for diagnosing DFO were generalized, and the majority only used plain radiographs a diagnosis
- Majority of the studies used wound healing as the primary outcome measure.
  - However, there are no study that states that a wound would fail to heal if there are underlying OM.
- There was no one guideline that the various authors seem to follow for the duration of antibiotic. There is a wide range of antibiotic durations ranges from 4 weeks to 70 weeks with success rate ranging from 17% to 97.3%.

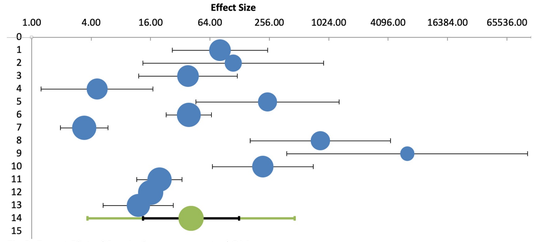



**Fig 3:** Forest Plot of Surgical management of OM

This meta-analysis suggested that surgical treatment is more favorable over medical management of DFO.

- Surgical intervention resulted in significant findings with a prediction interval suggesting that all future studies will share the same positive results.
- In medical management, there was 1 study with negative result and 2 with no significant finding with an overall prediction interval that indicated likelihood of no positive result in future studies.
- This suggests that surgical management for DFO will yield a more favorable outcome compared to medical management alone.

All 28 studies that we evaluated had different reference standards for diagnosing OM, successful treatment outcome, PAD, and neuropathy measurement. This made it difficult to compare the various studies results to one another. Additional properly design prospective studies with gold standard references for diagnosing OM are needed to help determine whether medical management of DFO can be successful without surgical intervention.

| # | Reference | Study | N | Duration of Antibiotic | Follow-up (months) | Reference Standard for OM | Reference Standard for Tx Success | % Success | QUADAS-2 Bias Risk |
|---|---|---|---|---|---|---|---|---|---|
| 1 | Niazi 2009 | Retrospective | 70 | 4 weeks | 10 | Exposed bone, PTB, red swollen toe with ulceration, chronic deep ulcer over bony prominence, sinus tract with purulence drainage | Eradication of infection with normal inflammatory markers, ulcer healing/stable ulcer | 90% | High |
| 2 | Akkurt 2017 | Retrospective | 23 | NR | 18 | Bone culture | Total cure of infection and OM at 12 weeks determined by MRI and clinical assessment | 91.30% | Low |
| 3 | Lesens 2015* | Retrospective | 35 | 10 ± 2 weeks | 21 ± 1 | Bone culture | 1) Complete healing of wound,<br>2) No SOI 6 months after completion of antibiotic therapy, and<br>3) A stable or improved bone on XR | 80% | Low |
| 4 | Larzo-Martinez 2014 | Prospective RCT | 22 | 10 days | NR | Probe to bone, XR | Complete epithelialization | 68% | High |
| 5 | Beieler 2012 | Retrospective | 50 | 42 days | 26 | • Combination of histopathology, exposed bone, XR changes, or MRI<br>• 88% confirmed by pathology<br>• 12% confirmed as above with no pathology obtained | No further treatment for OM needed | 94% | Low |
| 6 | Gauland 2011 | Retrospective | 232 | Intra-op vancomycin + gentamycin | NR | XR, MRI, CT, and/or Bone biopsy AND confirm bone biopsy of resected bone | Wound healed w/ no SOI and/or ESR, CRP, WBC normalized | 86.40% | Low |
| 7 | Kowalski 2011 | Retrospective | 111 | 19 days | 12 | Histology | No relapsed of OM via pathology or culture | 65% | Low |
| 8 | Aragon-Sanchez 2011 | Retrospective | 90 | NR | NR | Probe to bone and XR changes | Limb salvage = patient did not undergo a major amputation | 96.50% | Low |
| 9 | Aragon-Sanchez 2011 | Prospective | 81 | 36 days | 25.5 | NR | Complete epithelization | 98.8% | High |
| 10 | Aragon-Sanchez 2009 | Retrospective | 95 | NR | NR | Histology | Complete epithelization | 93.60% | Unclear |
| 11 | Aragon-Sanchez 2008 | Retrospective | 185 | NR | Until wound healed | Probe to bone and XR changes | 1) Healing w/ complete epithelialization of ulcer, AND/OR<br>2) "Surgical wound performed to operate the bone infection" | 81.8% | High |
| 12 | Henke 2005 | Retrospective | 51875 | NR | NR | NR | NR | 1) 56% healed ,2) 80%… limb salvage | High |
| 13 | Ha Van 1996 | Retrospective | 67 | 111 ± 121 days | NR | Probe to bone and XR changes | Complete epithelization | 78% | High |

**Table 2:** Studies for surgical management. XR = x-ray (plain); PTB = probe-to-bone; MRI = magnetic resonance imaging; CT = computerized tomography; SOI = sign of infection; OM = osteomyelitis; NR = not reported

| # | Reference | OR | 95% CI | Weight |
|---|---|---|---|---|
| 1 | Mauler | 0.04 | 0.01-0.25 | 4.02% |
| 2 | Lesens* | 93.84 | 25.06-351.37 | 4.99% |
| 3 | Tone | 3.45 | 1.36-8.77 | 5.87% |
| 4 | Larzo-Martinez* | 14.44 | 3.45-60.39 | 4.79% |
| 5 | Acharya | 4.09 | 2.44-6.88 | 6.66% |
| 6 | Mutluoglu | 1296 | 74.36-22586.51 | 2.39% |
| 7 | Valabhji | 9.47 | 3.87-23.18 | 5.95% |
| 8 | Jeffcoate | 1.97 | 1.16-3.36 | 6.64% |
| 9 | Senneville 2008 | 3.16 | 1.38-7.23 | 6.09% |
| 10 | Embril | 16.70 | 8.74-31.94 | 6.44% |
| 11 | Tice | 4.99 | 3.37-7.37 | 6.85% |
| 12 | Yadlapalli | 14.69 | 5.93-36.44 | 5.92% |
| 13 | Senneville 2001 | 10.56 | 2.03-54.84 | 4.37% |
| 14 | Pittet | 2.66 | 1.18-6.03 | 6.11% |
| 15 | Ha Van* | 1.72 | 0.86-3.42 | 6.37% |
| 16 | Venkatesan | 11.56 | 2.71-49.38 | 4.75% |
| 17 | Peterson | 3.31 | 1.14-9.56 | 5.60% |
| 18 | Bamberger | 1.27 | 0.58-2.78 | 6.18% |
| | Combined Effect | 5.25 | 2.26-12.17 | 100% |

**Table 3:** The odd ratios (OR) and study weight of medical management of osteomyelitis

| # | Reference | OR | 95% CI | Weight |
|---|---|---|---|---|
| 1 | Niazi | 81 | 26.59246.79 | 7.80% |
| 2 | Akkurt | 110.25 | 13.38-908.60 | 4.77% |
| 3 | Lesens* | 15.47 | 6.89-34.72 | 8.90% |
| 4 | Larzo-Martinez* | 4.59 | 1.24-16.96 | 7.20% |
| 5 | Beieler | 245.44 | 46.15-1305.44 | 5.91% |
| 6 | Gauland | 39.06 | 23.01-66.31 | 9.76% |
| 7 | Kowalski | 3.41 | 1.96-5.93 | 9.70% |
| 8 | Aragon-Sanchez 2011 | 841.00 | 163.33-4330.31 | 5.98% |
| 9 | Aragon-Sanchez 2011 | 6400.00 | 385.18-106339.01 | 3.25% |
| 10 | Aragon-Sanchez 2009 | 220.03 | 67.83-713.68 | 7.57% |
| 11 | Aragon-Sanchez 2008 | 19.72 | 11.63-33.44 | 9.77% |
| 12 | Henke | 16 | 15.52-16.49 | 10.54% |
| 13 | Ha Van* | 12.02 | 5.29-27.28 | 8.86% |
| | Combined Effect | 41.19 | 13.47-125.90 | 100% |

**Table 4:** The odd ratios (OR) and study weight of surgical management of osteomyelitis