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

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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 (χ^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, τ^2 and τ were calculated, where τ^2 reflects the variance of the true effect size. Both τ^2 and τ represent the true heterogeneity.

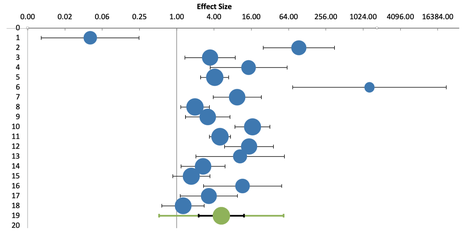

Fig 2: Forest Plot of Medical management of OM

#	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, 2) no SOI 6 months after completion of antibiotic therapy, and 3) a stable or improved bone on XR	87%	Low
3	Tone 2015	Prospective RCT	40	50% 6 weeks 50% 12 weeks	12	XR and Bone culture after at least 2 weeks of antibiotic-free period	complete and persistent (> 4 weeks) of: 1) healing of wound 2) absence of recurrent infection 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) 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) IV median length = 16 days (1-44 days)	12	Clinically based and XR changes 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: 1) Wound > 2 weeks over a bony prominence with an ulcer > 2cm sq or depth > 3mm, assoc. w/ PTB and/or 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: 1) (+) Xray change 2) (+) bone scan 3) visible or PTB 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. 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 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: 1) XR changes 2) clinical sign of inflammation 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

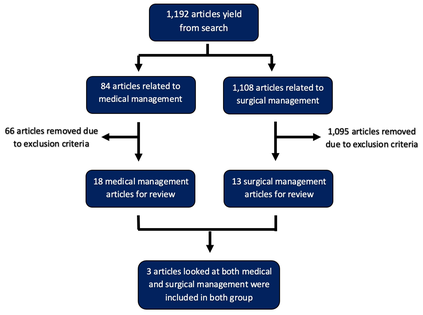

Fig 1: Result of search analysis. 31 articles qualified for review at the end after exclusion criteria were applied.

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. τ^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%.

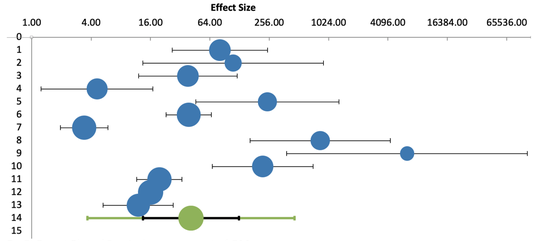

Fig 3: Forest Plot of Surgical management of OM

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, 2) No SOI 6 months after completion of antibiotic therapy, and 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 • 88% confirmed by pathology • 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 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