



## CLINICAL SUMMARY

---

---

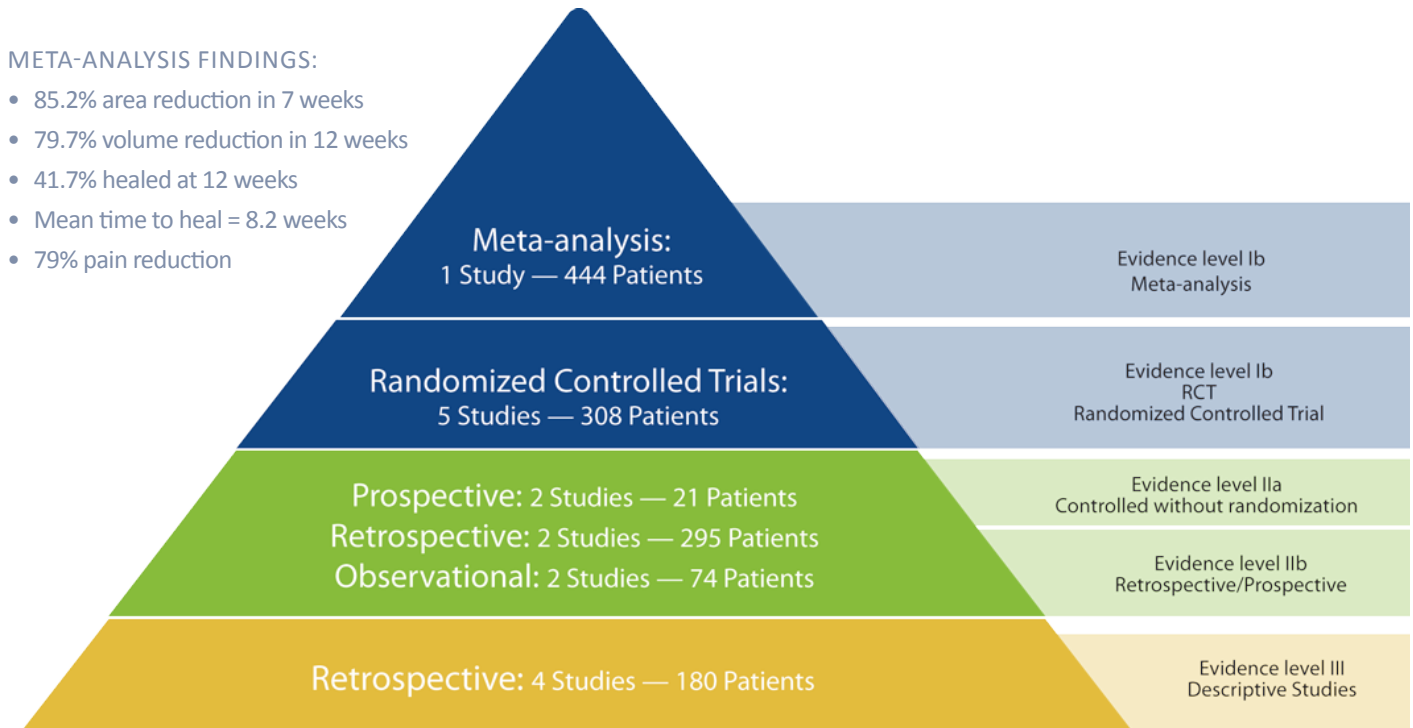
Many of the wound care products available today have limited clinical evidence to support their use. Celleration made the decision early on to invest in high quality clinical evidence that supports the appropriate use of MIST Therapy to assist medical professionals in their wound care treatment decisions.

## CLINICAL EVIDENCE LEVEL I-III SUMMARY

MIST Therapy was introduced into the market in late 2004 and has been investigated in a variety of Level I-III Clinical Studies including one (1) meta-analysis, five (5) randomized controlled trials, two (2) prospective, six (6) retrospective, and two (2) observational studies.

Few wound care technologies have the clinical evidence to support a meta-analysis. In the meta-analysis using only MIST Therapy ultrasound clinical data, eight (8) peer-reviewed studies with consistent designs for treatment and control wound groups were pooled to review the effects of MIST Therapy on healing time, wound size, volume, and pain. The authors concluded that “MIST Therapy demonstrates remarkable consistency of reduction in wound area, volume, pain and healing times across a wide range of wounds.”

### SUMMARY OF MIST THERAPY LEVEL I-III CLINICAL DATA



**The results of these Level I-III studies demonstrate accelerated wound healing in patients with multiple comorbidities. When compared to standard of care results, MIST Therapy provides nearly twice the healing in the same period of time as traditional Standard of Care (SOC). See tables on following pages for more details.**

**TABLE OF CLINICAL EVIDENCE LEVEL I STUDY DETAILS**

LEVEL OF EVIDENCE	PUBLICATION AUTHOR JOURNAL	WOUND POPULATION	MEASUREMENT	MIST RESULT	SOC RESULT	TREATMENT DURATION	STATISTICS
I b	Noncontact Low-Frequency Ultrasound Therapy in the Treatment of Chronic Wounds: A Meta-Analysis  Driver VR, Yao M, Miller CJ  Wound Regeneration and Repair 2011	N* = 444 (463 wounds)	Wound Closure (N=429)	41.7%	*24%	12 weeks	95% CI (Confidence Interval)
			Wound Area Reduction (N=188)	85.2% reduction	Not reported	Mean 7 weeks	95% CI
		Diabetic Foot, Ischemic, Neuropathic, Venous, Multifactorial Etiology, Pressure, Surgical, Traumatic	Wound Volume Reduction (N=278)	79.7% reduction	Not reported	Mean 12 weeks	95% CI
			Pain Reduction (N=139)	79% reduction	Not reported	From Baseline	Not reported
I b  NEW	A Prospective, Randomized, Controlled Trial Comparing the Effects of Noncontact, Low-Frequency Ultrasound to Standard Care in Healing Venous Leg Ulcers  Gibbons GW, Orgill DP, Serena TE, Novoung A, O'Connell JB, Li WW, Driver VR  Ostomy and Wound Management 2015	N = 81	Mean % Wound Area Reduction	61.6% reduction	45% reduction	4 weeks	p=0.02
		Venous Leg Ulcers	Pain VAS Measurement	80% reduction	20% reduction		p=0.01
I b	High-Frequency and Noncontact Low-Frequency Ultrasound Therapy for Venous Leg Ulcer Treatment: A Randomized, Controlled Study  Olyaie M, Rad FS, Elahifar MA, Garkaz A, Mahsa G  Ostomy and Wound Management 2013	N = 90	Wound Area Reduction	72.8% at 4 months	55.4% at 4 months	12 weeks followed by SOC	p=0.04
			Mean time to healing in months	6.65	8.5		p<0.05
		Venous Leg Ulcers	Pain Reduction	47.1% reduction at 4 months	17.7% reduction at 4 months		p=0.001
I b	A Pilot Study Evaluating Noncontact Low Frequency Ultrasound on Diabetic Foot Ulcers and Underlying Molecular Mechanisms  Yao M, Hasturk H, Kantarci A, Gu G, Garcia-Lavin S, Fabbi M, Park N, Hayashi, H, Attala K, French M, Driver V  International Wound Care Journal 2012	N = 12	Wound Area Reduction	86% reduction	39% reduction	4 weeks	p<0.05
I b	Treatment of Ischemic Wounds with Noncontact, Low-Frequency Ultrasound: The Mayo Clinic Experience, 2004-2006  Kavros SJ, Miller JL, Hanna SW  Advances in Skin & Wound Care 2007	N = 70	>50% Wound Area Reduction	63% achieved >50% reduction	29% achieved >50% reduction	12 weeks	p<0.001
		Ischemic, Neuropathic, Venous, Multifactorial					
I b	Ultrasound Therapy for Recalcitrant Diabetic Foot Ulcers: Results of a Randomized, Double-Blind, Controlled Multicenter Study  Ennis WJ, Formann P, Mozen N, Massey J, Conner-Kerr T, Meneses P  Ostomy & Wound Management 2005	N = 55	Wound Closure	40.7%	14.3%	12 weeks	p<0.0366
		Diabetic Foot Ulcers					

\*Total patient population from 8 studies = 519 (444 treated with MIST), 538 wounds (463 treated with MIST)

\*\*Margolis meta-analysis of standard of care treatments for DFU's was discussed in the article and used for comparison to MIST results.

**TABLE OF CLINICAL EVIDENCE LEVEL II STUDY DETAILS**

LEVEL OF EVIDENCE	PUBLICATION AUTHOR JOURNAL	WOUND POPULATION	MEASUREMENT	MIST RESULT	SOC RESULT	TREATMENT DURATION	STATISTICS
II a	A Prospective Pilot Study of Ultrasound Therapy Effectiveness in Refractory Venous Leg Ulcers  Escandon J, Vivas AC, Perez R, Kirsner R, Davis S  International Wound Journal 2012	N = 10  Venous Leg Ulcers	Wound Area Reduction	45% reduction	Failure to improve in previous 30 days	4 weeks	p<0.0039
II a	The Impact of Noncontact, Nonthermal, Low-Frequency Ultrasound on Bacterial Counts in Experimental and Chronic Wounds  Serena T, Lee SK, Lam K, Attar P, Meneses P, Ennis W  Ostomy Wound Management 2009	N = 11  Pressure Ulcers (Stage III)	Wound Volume Reduction  Wound Area Reduction	20% reduction  26% reduction	NA	2 weeks	Not reported
II b	Effects of Noncontact Low-Frequency Ultrasound on Healing of Suspected Deep Tissue Injury: A Retrospective Analysis  Honaker JS, Forston MR, Davis EA, Wiesner MW, Morgan JA  International Wound Care Journal 2012	N = 85 (127 DTIs)  Deep Tissue Injuries (Pressure Ulcers)	Wound Evolution/Resolution at hospital discharge  Severity Scale Assessment	Resolved 18% Stage II 62% DTI 5% Stage III, IV unstageable 15%	2% 20% 30% 48%	10 MIST Treatments over 21 days	Not reported  p<0.000
II b	Expedited Wound Healing with Noncontact, Low-Frequency Ultrasound Therapy in Chronic Wounds: A Retrospective Analysis  Kavros SJ, Liedl DA, Boon, AJ, Miller JL, Hobbs JA, Andrews KL  Advances in Skin and Wound Care 2008	N = 210  Ischemic, Venous, Neuropathic, Multifactorial	Wound Closure	53% in mean of 147 days	32% in mean of 134 days	SOC followed by 12 weeks MIST treatment then SOC	p = 0.0009
II b	Use of Noncontact Low-Frequency Ultrasound in the Treatment of Chronic Foot and Leg Ulcerations  Kavros SJ, Schenck EC  J of American Podiatric Medical Assn 2007	N = 51  Chronic Lower Leg and Foot Ulcers, Multifactorial, Arterial, Diabetic	Wound Closure  Wound Volume Reduction	51%  94.9±9.8% reduction	0% patients were treated with SOC prior to starting MIST  37.3±18.6% reduction	MIST mean 5.5±2.8 weeks  SOC mean 9.8±5.5 weeks	p<0.05  p<0.0001
II b	Evaluation of Clinical Effectiveness of MIST Ultrasound Therapy for the Healing of Chronic Wounds  Ennis WJ, Valdes W, Gainer M, Meneses P.  Advances in Skin and Wound Care 2006	N = 23 (29 wounds)  Diabetic, Ischemic, Venous, Pressure, Post-operative, Inflammatory	Wound Closure	MIST only 69%  MIST assisted* 73.3%	<15% area reduction in 2 week prior to MIST	6.82 weeks  10.47 weeks	Not reported  Not reported

\*addition of Apligraf

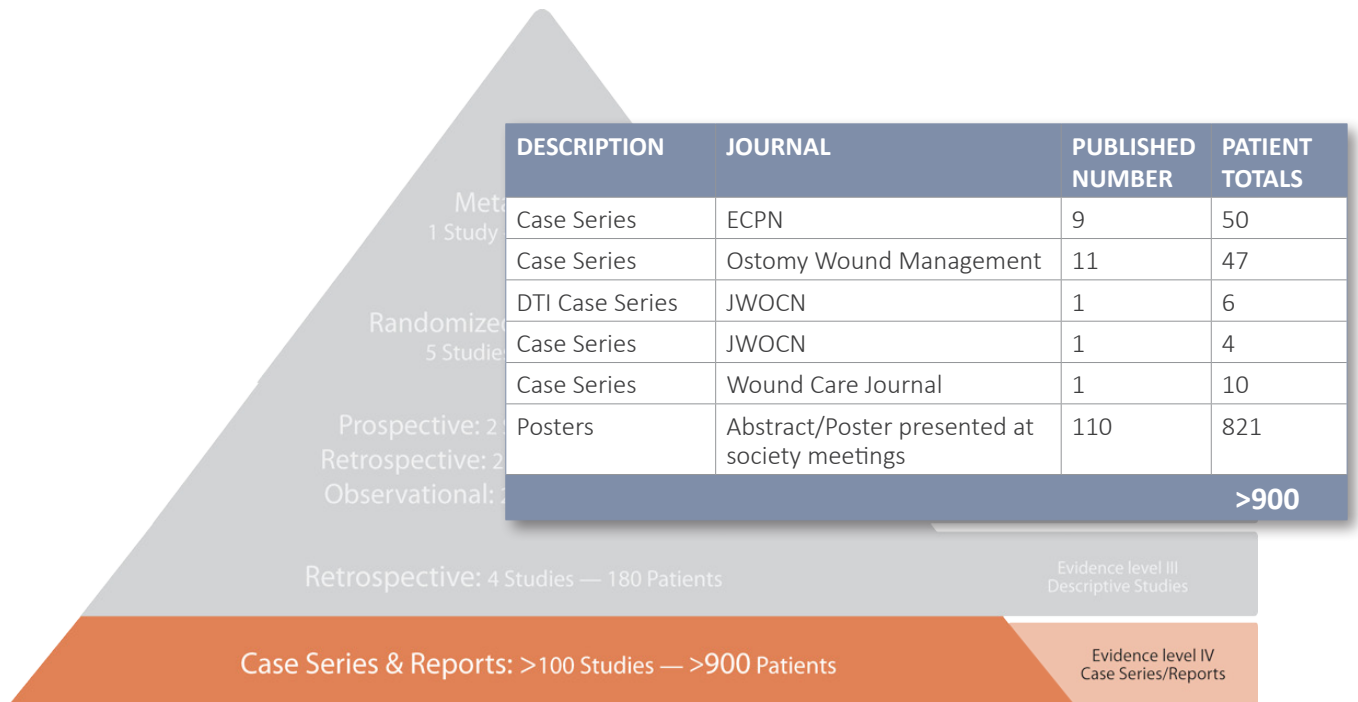
**TABLE OF CLINICAL EVIDENCE LEVEL III STUDY DETAILS**

LEVEL OF EVIDENCE	PUBLICATION AUTHOR JOURNAL	WOUND POPULATION	MEASUREMENT	MIST RESULT	SOC RESULT	TREATMENT DURATION	STATISTICS
III	Adjuvant Use of Acoustic Pressure Wound Therapy* for Treatment of Chronic Wounds  Cole PS, Quisberg J, Melin MM  J Wound Ostomy Continence Nursing 2009	N = 41 (52 wounds)	Wound Closure	38%	<15% wound area reduction in 2 weeks prior to MIST	Mean 6.8 weeks	Not reported
			Wound Area Reduction	88% reduction		Mean 7.6 weeks	p<0.0001
		Wound Volume Reduction	100% reduction				p<0.0001
		Pressure, Venous, Arterial, Surgical, Traumatic, other	Pain VAS Measurement	2.9 reduction	NA		p<0.0001
III	A Retrospective Analysis of Acoustic Pressure Wound Therapy: Effects on the Healing Progression of Chronic Wounds  Haan J, Lucich S  J American College of Certified Wound Specialists 2009	N = 48 (50 wounds)	Wound Closure	24%	<15% wound area reduction in 2 weeks prior to MIST	Mean 4.2 weeks	Not reported
		Pressure, Venous, Arterial, Surgical, Traumatic, Neuropathic, other	Wound Area Reduction	92% reduction		Mean 5.5 weeks	p<0.0001
			Pain VAS Measurement	1.8 reduction	NA		p<0.0001
III	Noncontact Ultrasound Therapy for Adjunctive Treatment of Nonhealing Wounds: Retrospective Analysis  Bell AL, Cavorsi J  PT Journal 2008	N = 76	Wound Closure	18%	<15% reduction in 2 weeks prior to MIST	Median 3.6 weeks	Not reported
			Wound Area Reduction	79% reduction		Median 4.3 weeks	p<0.0001
		Pressure, Venous (28), Arterial, Surgical/Traumatic (25), other	Pain VAS Measurement	1.8 reduction	NA		p=0.001
III	The Effect of Noncontact, Low-Intensity, Low-Frequency Therapeutic Ultrasound on Lower-Extremity Chronic Wound Pain: A Retrospective Chart Review  Gehling ML, Samies JH  Ostomy Wound Management 2007	N = 15  Venous, Ischemia, Sickle cell	Pain VAS Measurement	80% reduction  (8.07±1.91 to 1.67±1.76) VAS	Baseline	2-4 weeks	p = 0.0003

\*Acoustic Pressure Wound Therapy = Noncontact Low Frequency Ultrasound = MIST Therapy  
VAS Measurement = Visual Analog Scale used to assess pain- 10 point scale

## CLINICAL EVIDENCE LEVEL IV SUMMARY - PUBLISHED CASE SERIES AND REPORTS

Over 900 patients have been studied in peer reviewed case series/reports showing successful outcomes with MIST Therapy across all care settings.



These cases include patients with a wide variety of wound types including:

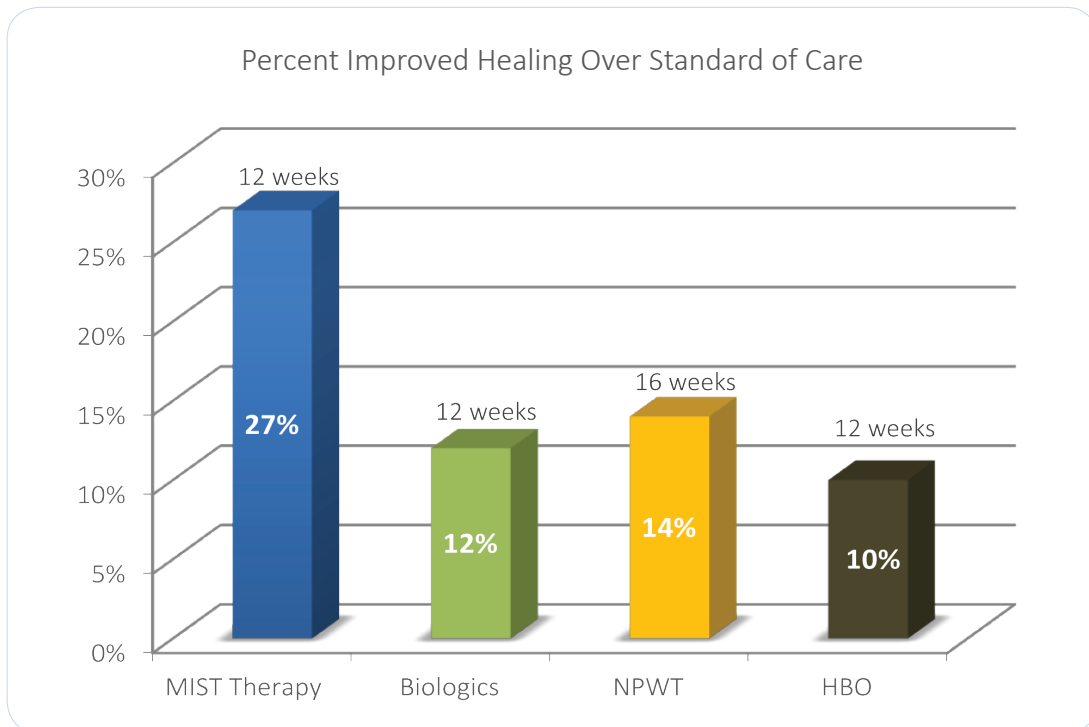
- Amputation Incisions
- Arterial Ulcers
- Burns
- Calciphylaxis
- Graft Preparation
- Deep Tissue Injuries
- Dehisced Wounds
- Diabetic Ulcers
- Donor Sites
- Exposed Tendons
- Fungal
- IV Infiltrates
- Medical Device Induced Wounds
- Necrotizing Fasciitis
- Perirectal Abscess
- Pilonidal Cysts
- Pressure Ulcers
- Pyoderma Gangrenosum
- Sickle Cell
- Surgical Wounds
- Traumatic Wounds
- Undermining/Tunnels
- Vascular Ulcers
- Wound Matrix Product

**As wound care specialists have gained a better understanding MIST Therapy's mechanism of action, the versatility of the system has allowed them to apply this technology to a number of challenging wound types.**

## MIST THERAPY COMPARED TO OTHER ADVANCED WOUND CARE TREATMENTS

It can be difficult to compare one advanced wound care treatment to another as very little comparative data exists today. In addition, many of the studies that exist have been completed in different patient populations with different wound types.

To evaluate how MIST Therapy compared to other advanced wound care treatments, we looked at randomized control trials in a single wound type- diabetic foot ulcers (all studies compared treatment arm to standard of care). To control for differences in patient populations, we evaluated the difference in healing rates between the treatment group and the control group.



	Weeks Treated	Treatment Group % healed	Control Group % healed	Difference	Study
<b>MIST Therapy</b>	<b>12</b>	<b>41.7%</b>	<b>14.3%</b>	<b>27.4%</b>	Ennis 2005, Celleration MIST Therapy (n=55)
Biologics	12	30%	18%	12%	Marston 2003, Smith and Nephew- Dermagraft (n=314)
NPWT	16	43%	29%	14%	Blume 2008, KCI- VAC (n=342)
HBO	12	12%	2%	10%	Londahl 2010, Independent Study (n=94)

**All of the advanced wound care treatments demonstrated faster healing rates in the same period of time when compared to the standard of care arm. However, MIST Therapy provided twice the benefit when compared to the other advanced wound care treatments.**