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Correlation between Digital Planimetry and a Manual Method in the Measurement of Lesion Size in a Phase 3 Acute Bacterial Skin and Skin Structure Infection (ABSSSI) Study

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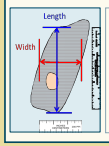
INTRODUCTION

New FDA guidelines for the development of antibiotics to treat Acute Bacterial Skin & Skin Structure Infections (ABSSSI) focus on the assessment of lesion size and cessation of spread at 48-72 hrs as the primary component of efficacy determination. Methods to accurately measure changes in lesion size are critical to assess treatment effect. One of the simplest methods of measuring wound size calculates the area by manual measurement of longest length by widest width (*L x W*) using a ruler or tape measure. This method has limitations due to subjective interpretation and interobserver variability. Additionally, the *L x W* manual measurement is accurate mathematically only for square and rectangular shaped lesions. Even with simple *L x W* measurement methods a number of different strategies can be employed yielding different results with more or less variability. The longest length head-to-toe, and the widest width side-to-side (perpendicular to length) has been shown to be the least variable of these manual methods. Digital planimetry has also been used to measure wound healing. Planimetry is the measurement of areas and perimeters by tracing the boundaries. PictZar™ CDM Software provides a unique method of calibrating digitally captured images without having to know the distance between the camera lens and the subject. We set out to compare digital planimetry with the more traditional 2-dimensional linear wound measurement using *L x W* manual measurement (head-to-toe orientation).

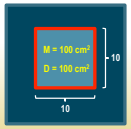
METHODS

We are currently conducting a Phase 3, randomized, double-blind study of 6-days tedizolid phosphate (previously torezolid phosphate, TR-701) vs 10-days linezolid in ABSSSI. The data presented herein are from this ongoing study and remain blinded as to study treatment. Investigators were instructed to mark and outline the edge of erythema from severe abscesses, cellulitis and infected wounds using a surgical marker. Measurement of the erythema was to be in a head-to-toe orientation (as described below), and measurements were recorded in source documents and in the eCRF. Lesion surface area (cm^2) is automatically calculated by the e-CRF for the manual measurements. The sites were also instructed to capture digital photographic images of the lesions at the Screening, Day 3, and End-of-Therapy visits. If lesions were 3-dimensional in nature wrapping around the circumference of body parts (arms, legs, torso), then multiple images were to be captured perpendicular to the body surface. The digital images were uploaded by site personnel into the clinical trial database. Once uploaded, the digital images were organized and processed using Photoshop® (Adobe) image editing software (cropping, levels, curves, color correction, image rotation, and sharpening tools). After the images were enhanced to provide the best possible image to analyze, PictZar®-CDM digital planimetry wound measurement software developed by Dr. Martin Wendelken was used to assess lesion size. A comparison of the results of manual measurement at the bedside by site personnel versus an analysis of lesion size via digital planimetry is presented.



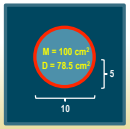
Investigators were instructed to measure erythema surrounding the wound in a head-to-toe orientation by measuring the longest length head-to-toe and then the widest width perpendicular to that length. Measurements were captured in source documents and surface areas (cm^2) were calculated by the e-CRF. Additionally, for abscesses and wounds, measurements of the greatest distance from the margin of the wound/abscess to the perimeter of the surrounding erythema or cellulitis were captured.

METHODOLOGY



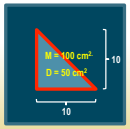
Area of RECTANGLE = L x W

A 2-dimensional square or rectangle measured manually (M) and digitally (D) should be equivalent. In this example, a 10 cm x 10 cm lesion will generate an area of 100 cm^2 by both methods.



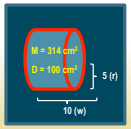
Area of CIRCLE = πr^2

A 2-dimensional circular lesion measured manually will overestimate the true size of the lesion. In this case, digital planimetry will give a more accurate estimate of the true surface area of a circle with a 10 cm diameter (78.5 cm^2).



Area of TRIANGLE = ½ W x L

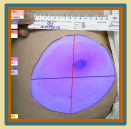
A 2-dimensional lesion of triangular shape will significantly be overestimated when measured manually using L x W coordinates. Digital planimetry provides a more accurate measurement, 50% of the manual method.



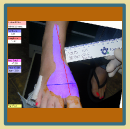
Area of CYLINDER = $2\pi rw$

The external surface area of an arm or leg (represented as a cylinder) provides one of the most difficult measurements, requiring multiple photographic views translating 2-dimensional images into 3-dimensional structures.

Investigators were instructed to measure lesions in a head-to-toe orientation providing length x width measurements that were used to calculate the surface area. Disposable paper rulers were used and also provided a scale of reference for the digital planimetry.



The shaded blue region is that outlined by the pen using a digital tablet while observing the image on a computer screen. PictZar software calculates the area by counting pixels after the image has been scaled with the ruler the Investigator uses manually.



Translating a 2-dimensional photographic image into an accurate measurement of a 3-dimensional structure has some inherent limitations if adequate controls are not in place. Ruler placement, focus, viewing angle and exposure can all adversely affect the TA.

The external surface area of cellulitis presenting on this patient's leg requires multiple photographic image views (preferably 4 views) to adequately capture the 3-dimensional total surface area of what could be considered a cylindrically shaped lesion.

DATA

COMBINED

		Screening Measurements					Screening to 48-72 Hr Visit Number of Patients (%)								Screening to End-of-Therapy					
	n	Mean	Mean SD	Median	Min	Max	Cessation of Spread	%	20% Decrease from Baseline	%	30% Decrease from Baseline	%	40% Decrease from Baseline	%	n	50% Decrease from Baseline	%	75% Decrease from Baseline	%	90% Decrease from Baseline	%
Area Measured Manually	**292**	254	240	195	27	2030	272	93.2%	256	87.7%	241	82.5%	207	70.9%	275	265	96.4%	262	95.3%	242	88.0%
Area Measured Digitally	**292**	172	174	131	18	1975	275	94.2%	181	62.0%	132	45.2%	83	28.4%	253	242	95.7%	238	94.1%	207	81.8%
Delta (Δ)		82	66	64	9	55		-1.0%		25.7%		37.3%		42.5%			0.7%		1.2%		6.2%

ABSCESS

		Screening Measurements					Screening to 48-72 Hr Visit Number of Patients (%)								Screening to End-of-Therapy					
	n	Mean	Mean SD	Median	Min	Max	Cessation of Spread	%	20% Decrease from Baseline	%	30% Decrease from Baseline	%	40% Decrease from Baseline	%	n	50% Decrease from Baseline	%	75% Decrease from Baseline	%	90% Decrease from Baseline	%
Area Measured Manually	**123**	228	229	184	27	1847	119	96.7%	116	94.3%	110	89.4%	96	78.0%	116	112	96.6%	110	94.8%	103	88.0%
Area Measured Digitally	**123**	153	136	126	18	932	119	96.7%	78	63.4%	59	48.0%	28	22.8%	106	101	95.3%	99	93.4%	87	82.1%
Delta (Δ)		75	93	58	9	915		0.0%		30.9%		41.5%		55.3%			1.3%		1.4%		5.9%

CELLULITIS

		Screening Measurements					Screening to 48-72 Hr Visit Number of Patients (%)								Screening to End-of-Therapy					
	N	Mean	Mean SD	Median	Min	Max	Cessation of Spread	%	20% Decrease from Baseline	%	30% Decrease from Baseline	%	40% Decrease from Baseline	%	n	50% Decrease from Baseline	%	75% Decrease from Baseline	%	90% Decrease from Baseline	%
Area Measured Manually	**100**	299	298	202	77	2030	86	86.0%	77	77.0%	71	71.0%	57	57.0%	94	87	92.6%	86	91.5%	79	84.0%
Area Measured Digitally	**100**	209	243	140	31	1975	88	88.0%	60	60.0%	44	44.0%	32	32.0%	89	84	94.4%	82	92.1%	73	82.0%
Delta (Δ)		90	55	62	46	55		-2.0%		17.0%		27.0%		25.0%			-1.8%		-0.6%		2.0%

WOUND

		Screening Measurements					Screening to 48-72 Hr Visit Number of Patients (%)								Screening to End-of-Therapy					
	n	Mean	Mean SD	Median	Min	Max	Cessation of Spread	%	20% Decrease from Baseline	%	30% Decrease from Baseline	%	40% Decrease from Baseline	%	n	50% Decrease from Baseline	%	75% Decrease from Baseline	%	90% Decrease from Baseline	%
Area Measured Manually	**67**	237	139	196	72	714	65	97.0%	61	91.0%	58	86.6%	52	77.6%	65	65	100.0%	65	100.0%	59	90.8%
Area Measured Digitally	**67**	154	92	142	33	472	66	98.5%	43	64.2%	29	43.3%	23	34.3%	57	56	98.2%	56	98.2%	46	80.7%
Delta (Δ)		84	47	54	39	242		-1.5%		26.9%		43.3%		43.3%			1.8%		1.8%		10.1%

OBSERVATIONS

- Ability of site personnel to adequately capture photographic images of sufficient quality to analyze by digital planimetry is essential
- Correct placement of a ruler in the same plane as the lesion is mandatory to accurately scale a digital image using the planimetry software
- Approximately 25% of patients presented with lesions at Screening that required multiple images taken at various viewing angles to adequately describe the 3-dimensional nature of the lesion

RESULTS

- At Baseline, digital planimetry tends to provide area size measurements ~1/3 smaller than manual measurements
- At the 48-72 hour visit the two methods yielded comparable results in assessing cessation of spread of the lesion
- High rates of response (as measured by cessation of spread) were observed at 48-72 hours, though higher for abscesses (~97%) and wound Infections (~97%) than for cellulitis (~86%)
- At the 48-72 hour visit cellulitis lesions decrease more slowly than abscess and wound infection lesions
- For all 3 lesion types, the difference between the 2 methods generally tends to increase in parallel with the % decrease from baseline
- At EOT visit (≤Day11): Reduction in lesion size was fairly comparable between the two methods
- Both methods provide comparable data (81.8% to 88.0%) of patients with all types of ABSSSI presenting a 90% reduction in lesion size at End-of-Therapy

CONCLUSIONS

- At the 48-72 hour visit cellulitis lesions decrease more slowly than abscesses and wound infection lesions
- The ability to assess cessation of spread is comparable between manual and digital planimetry methods
- At EOT visit both methods provide comparable data with 82 to 88% of patients presenting a 90% reduction in lesion size (all lesion types)

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- Rogers, et al. Digital Planimetry in More Accurate Wound Measurements: A Comparison to Stallard Ruler Measurements. J of Diabetes Sci and Tech. 2010; 4:799-802
- Langemo, et al. Measuring Wound Length, Width, and Area: Which Technique?. Adv Skin Wound Care. 2008; 21:42-5