SY038

Old antibiotics with a new life

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Minocycline and rifampicin: achievements and prospects

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Topics

- Rationale for the use of oral tetracyclines to treat MRSA
- Pre-clinical PK-PD of minocycline and combination with rifampicin
- Clinical trial data with minocycline plus rifampicin in MRSA infection
- Conclusions

Rationale for tetracycline use in MRSA

- Many IV drugs available for MRSA therapy (telavancin, oritavancin, dalbavancin, ceftobiprole, ceftaroline, tedizolid, eravacycline, licenced or under review)

- Few oral therapies which have undergone clinical trials (linezolid, tedizolid, co-trimoxazole) but many others used clinically

- Minocycline plus rifampicin is widely used orally to treat MRSA in Europe (Dryden et al, 2010)

- The combination has been used to eradicate MRSA carriage (Darouiche et al, 1991) but no clinical trials have been performed.

In vitro PK-PD studies

Dilutional single compartment in vitro pK model

- Part 1: minocycline (BD) dose ranging based on 200mg dose (AUC 11mg/L.h)
- Part 2: minocycline + rifampicin 600mg OD (fCmax 1mg/L)
- 4 MRSA minocycline MICs 0.12 to 1mg/L plus ATCC *S.aureus* (MSSA)
- Inoculum 10^6 CFU/ml, simulations run for >72 hrs
- Endpoints – AUC/MIC targets and changes in population profiles

Determining the pharmacodynamic driver

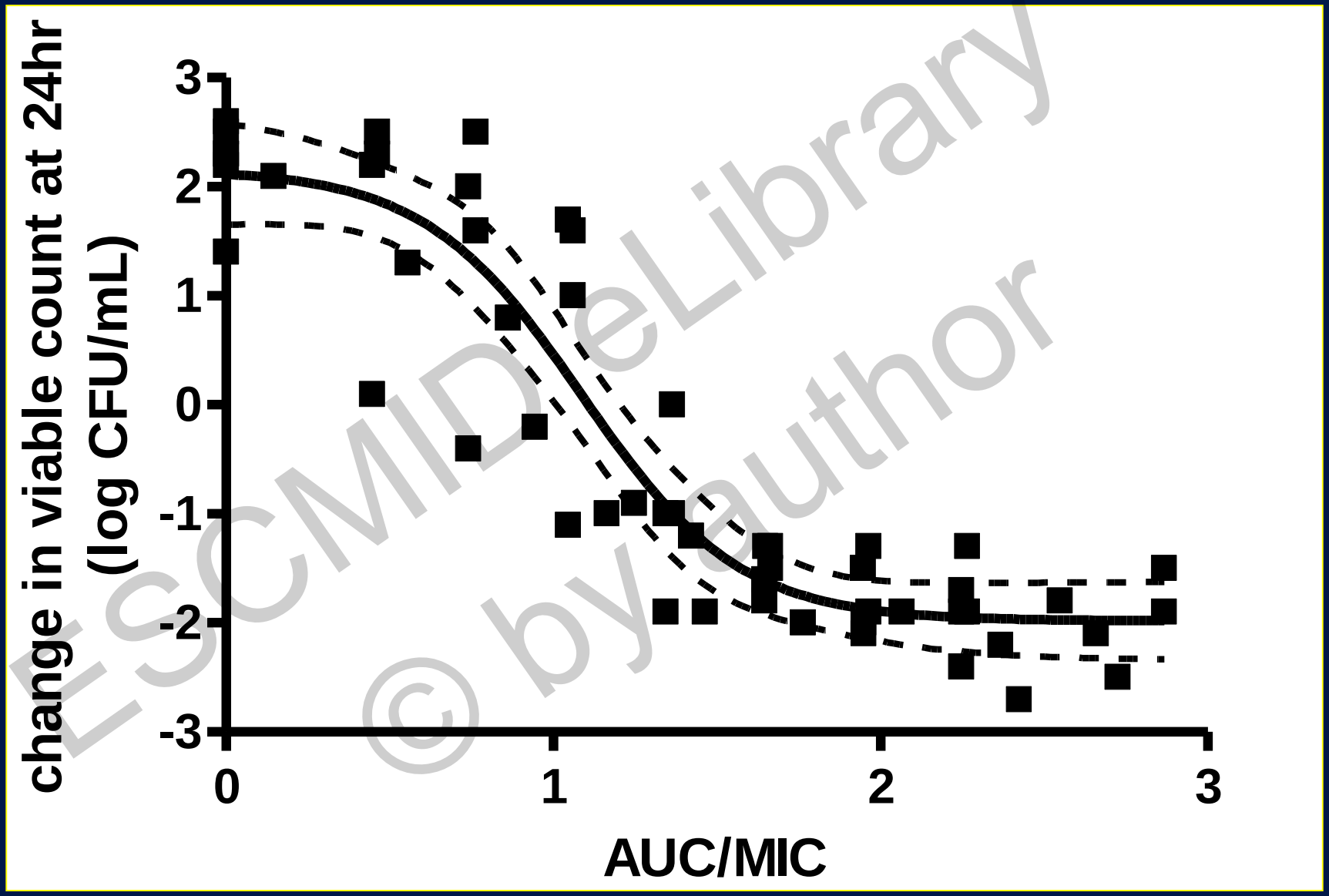
- **hollow fibre system, 1 strain *S.aureus* minocycline MIC 0.05mg/L**

measure of antibacterial effect	dosing regimen			
	67mg TDS	100mg BD	200mg OD	P value
AUBKC(24)	71 ± 1	80 ± 2	74 ± 3	0.24
log drop at 24h (d24)	-1.7 ± 0.1	-1.5 ± 0.3	-1.6 ± 0.1	0.29
T99.9(h)	>24	>24	>24	>0.05

PD index	R^2 of sigmoid	
	AUBKC	d24
AUC/MIC	0.92	0.87
Cmax/MIC	0.75	0.51
T>MIC	0.63	0.41

Bowker et al, 2005

Exposure response relationship for minocycline against MRSA



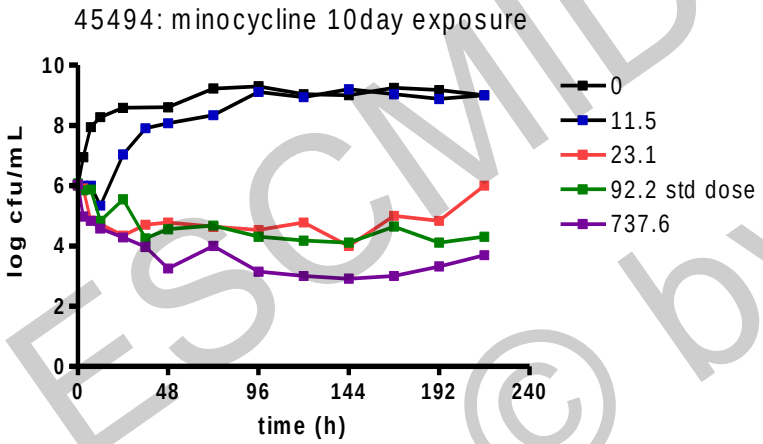
fAUC/MIC ratios required for bacteriostatic and cidal effects for minocycline against MRSA

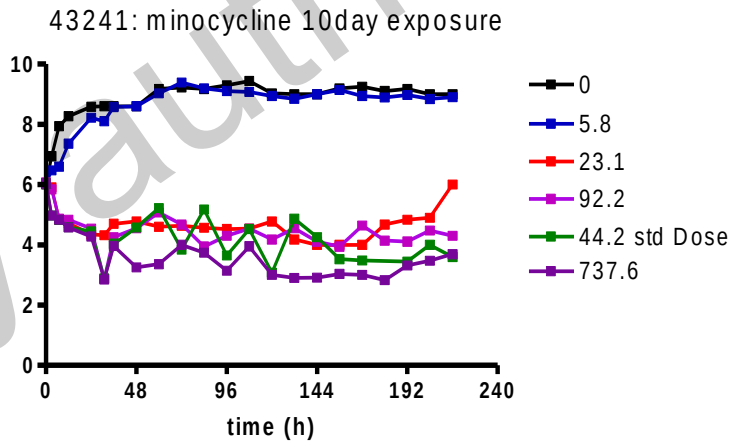
strain	MIC (mg/L)	fAUC/MIC for 24hr static effect	24hr -1 log drop	24hr -2 log drop	fAUC/MIC for 72hr static effect	72hr -1 log drop	72hr -2 log drop
43241	0.25	11.2	20.5	41.5	13.9	20.1	31.7
33827	0.5	3.2	7.3	>200	10.3	13.9	19.5
ATCC 29213	0.19	9.0	17.4	51.2	29.8	56.6	105
45494	0.12	19.0	29.3	>200	38.5	47.7	>200
33922	1.0	19.2	38.2	>200	17.0	27.8	55.6
		12.3±6.8	22.5±11.8	-	21.5±11.2	33.2±18.4	-

Noel et al, 2013

10 day minocycline alone

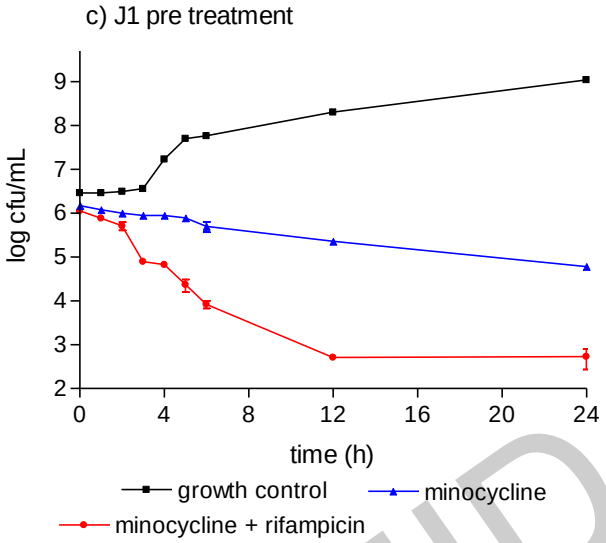
long term exposure (7-10d) for x2 MRSA strains 45494 MIC 0.12mg/L and 33827 MIC 0.5mg/L

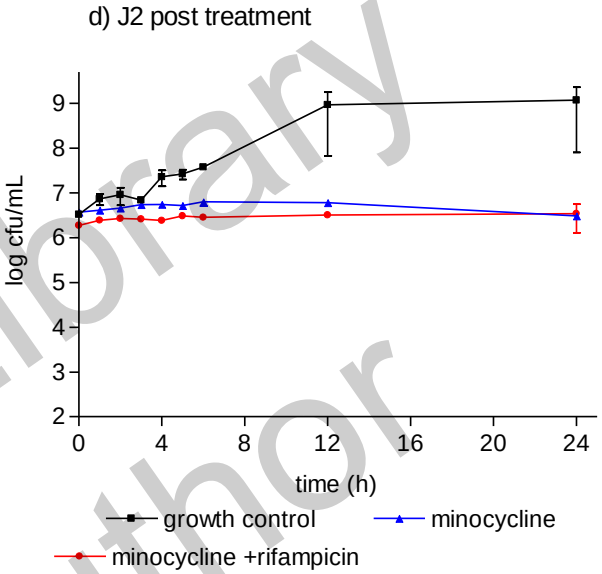




No EoR observed!

Minocycline and minocycline plus rifampicin against MRSA

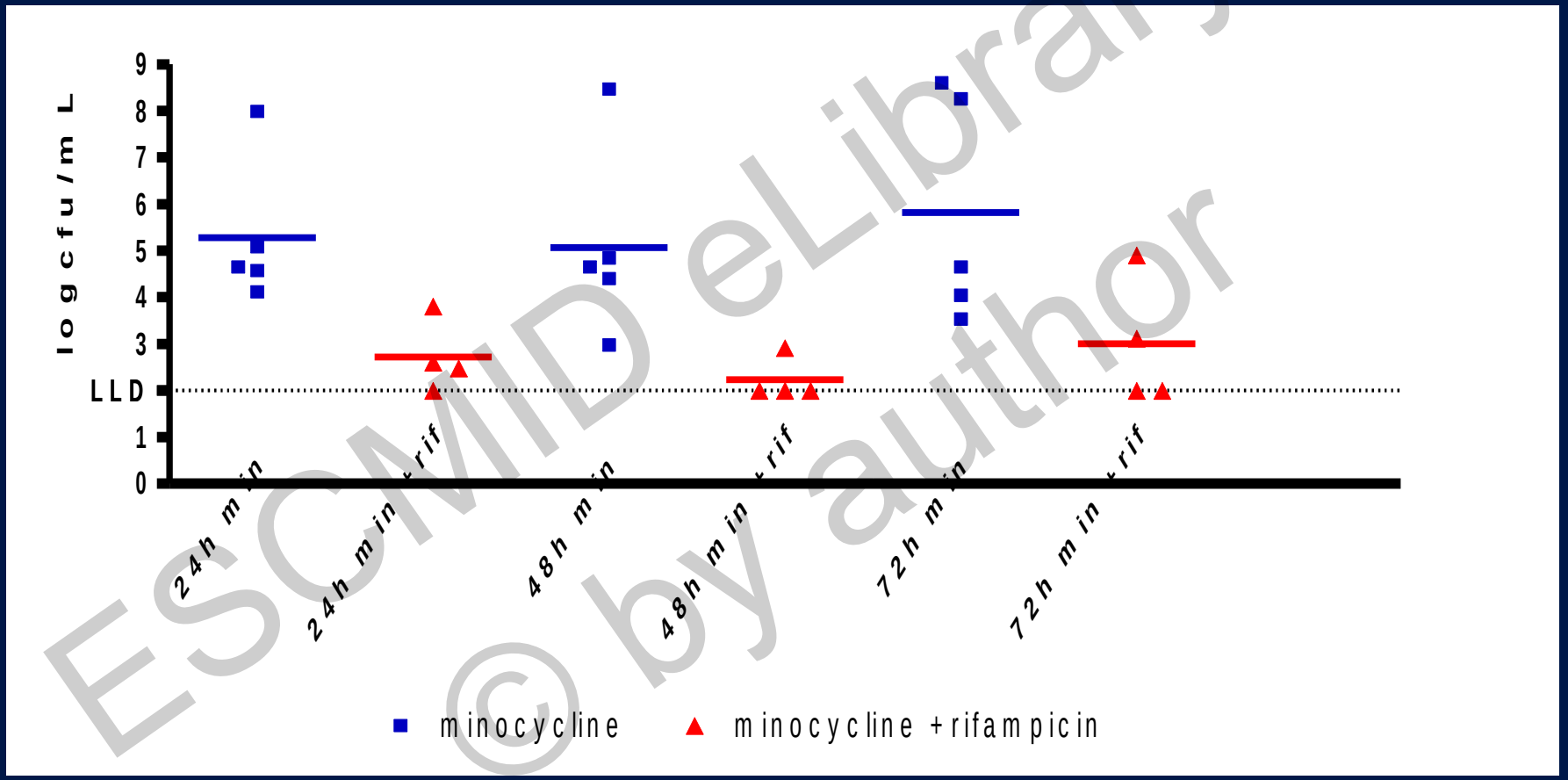




Strain	MIC (mg/L)	Antibacterial effect measure		
		log red. in viable count		AUBKC24 (log.cfu/ml.h
minocycline alone	Min MIC	**12h**	**24h**	
J1 (26910)	0.06	-0.8 ± 0.1	-1.6 ± 0.2	77.6 ± 2.8
J2 (31236)	**0.75**	**0.2 ± 0.1**	**-0.1 ± 0.1**	**98.4 ± 0.3**
minocycline +rifampicin	Rif MIC			
J1 (26910)	<0.016	-3.3 ± 0.1	-3.5 ± 0.4	32.7 ± 3.4
J2 (31236)	**>32**	**0.2 ± 0.04**	**-0.2 ± 0.1**	**98.8 ± 0.5**

Bowker et al 2008

Comparison of minocycline alone v minocycline plus rifampicin at the standard dose



Comparison of minocycline AUC/MICs with and without rifampicin: 72 hr effects

		72h AUC/MIC					
		Min			Min + Rif OD		
strain	MIC (mg/L)	static effect	-1 log drop	-2 log drop	static effect	-1 log drop	-2 log drop
45494**	0.12	36.5	47.7	>200	3.1	4.2	6.7
ATCC 29213**	0.19	29.8	56.6	105.0	5.5	6.4	7.2
43241	0.25	13.9	20.1	31.7	7.9	12.5	20.7
33827	0.50	10.3	13.9	19.5	0.6	1.2	1.8
33922	1.00	17.0	27.8	55.6	3.0	3.3	3.4
Mean +SD		21.5±11.2	33.2±18.4	52.9±37.6*	4.0±2.8	5.5±4.3	8.0±7.5

Dose range Minocycline, addition of Rifampicin fCmax 1mg/L

Emergence of resistance to rifampicin

	Growth on rifampicin MICx4 plates at 168h	
minocycline AUC/MIC	Experiment with colonies recovered	Count on MICx4 plates (log CFU/mL)
0	3/3	8.2 ± 0.1*
0.1-2.0	6/6	7.7 ± 1.6
2.1-4.0	4/4	7.1 ± 2.2
4.1-6.0	3/5	4.7 ± 3.2
6.1-12.0	4/4	4.6 ± 2.7
12.1-48.0	3/6	2.6
>48.0	1/7	3.0
growth controls	0/4	<2

*48 hr end point

Pharmacokinetics of oral minocycline

Dose	Frequency	Formulation	Cmax (mg/L)	t½ (h)	AUC (mg/L.h)	Ref
200mg	Single dose	-	3.1	17	43.9	Wood et al, 1975
200mg	Single dose	Tablet	3.5	12.9	47.6	Cartwright et al, 1975
		Capsule	3.6	13.1	46.1	

Protein binding 76% so $fAUC_{24}$ about 10mg/L.h

S.aureus MIC distribution (EUCAST)

MIC (mg/L)	Number	
≤0.03	40	
0.06	549	
0.12	1396	
0.25	322	← Minocycline clinical breakpoint (AUC/MIC ~10-20)
0.5	32	← Wild type cut off (EUCAST)
1.0	10	
2.0	14	
4.0	18	← Minocycline break point in combination with rifampicin (AUC/MIC~ 4-10)
8.0	10	
16.0	1	
≥32.0	0	

Pre-clinical PK-PD conclusions

- The dominant PDI for minocycline is AUC/MIC
- The minocycline AUC/MIC for 24hr static effect against MRSA is 5-20. This is a suitable translational target for cSSSI
- Addition of rifampicin increases the antibacterial effect, the AUC/MIC for static effect is reduced 5-7 fold
- Emergence of resistant to minocycline seems very rare
- Minocycline AUC/MIC >50 prevents emergence of resistance to rifampicin

Clinical Trial Data

Trial Objective

To demonstrate non-inferiority between patients, with acute complicated skin and skin structure infection (cSSSI) due to MRSA, treated with minocycline plus rifampicin compared to those treated with linezolid in terms of efficacy and safety.

Study Outcome

The minocycline+rifampicin combination was non-inferior in terms of:-

- clinical cure
- microbiological eradication
- safety
- Doses: minocycline (200mg/day); rifampicin (600mg/day); linezolid (1200mg/day)

Trial Description

- **Trial Design** - A prospective, open–label randomised controlled trial with a PK/PD evaluation

- **Sample size** - 195 patients, randomised in 2:1 ratio (min/rif : linezolid)

- **Setting** - 22 sites in Italy and Greece

- **Target population**
  - M/F patients, aged ≥ 18 years, with cSSSI due to MRSA requiring antimicrobial therapy

Primary Objective

The primary objective of the study was to demonstrate non-inferiority between patients treated with oral minocycline plus rifampicin and those patients treated with linezolid in terms of clinical cure at Test of Cure (TOC).

Secondary Objectives

Compare the safety profile between treatments

Compare eradication of MRSA from the site of infection between treatments

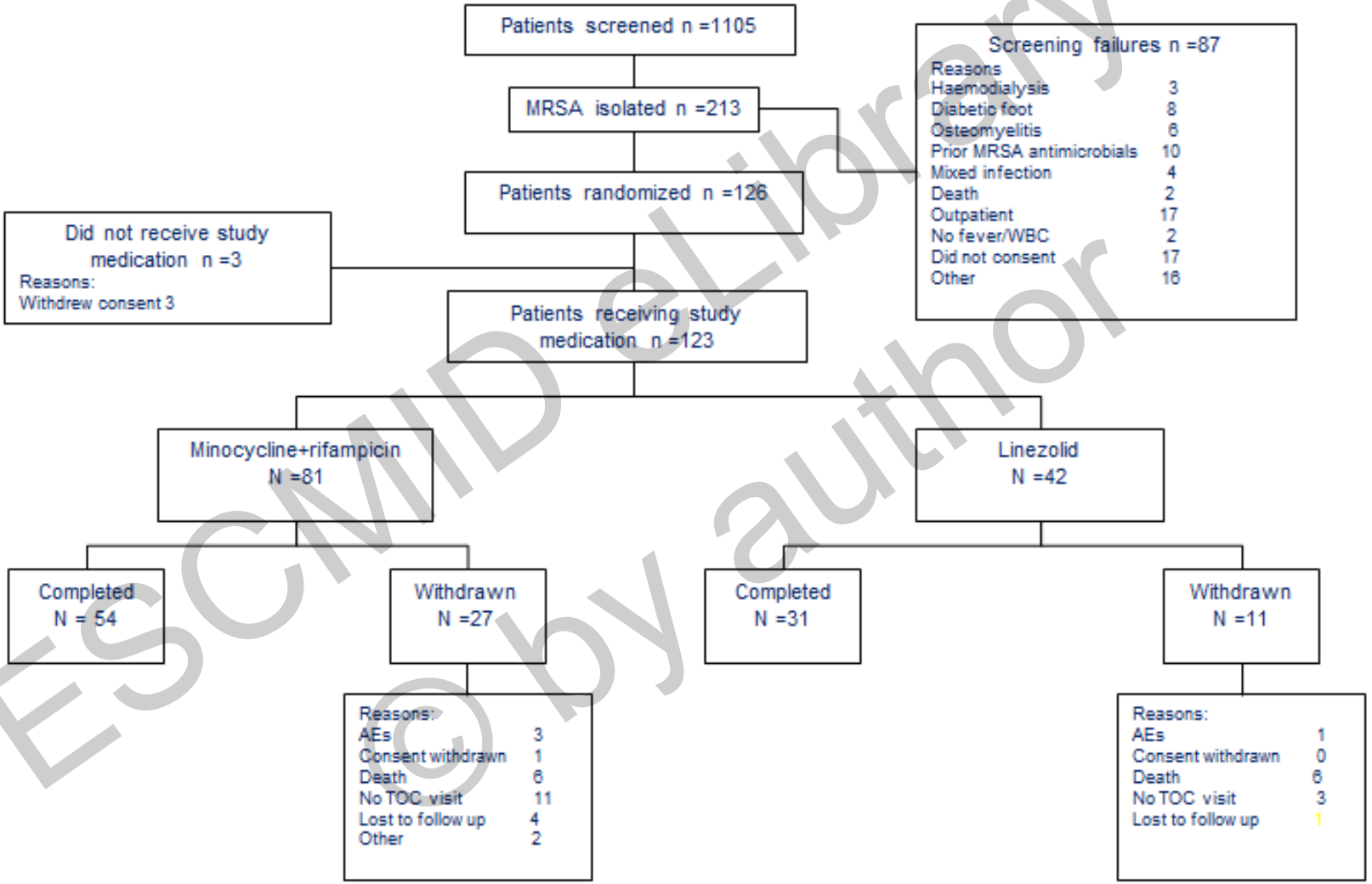
Planned Sample Size

- Non inferiority testing with a 5% significance level (one sided)
- 87% clinical cure rate for linezolid
- 2:1 ratio
- Non-inferiority limit of 15%
- Planned for 130 patients minocycline+rifampicin,
  65 patients linezolid
- Power = 0.9

Actual Sample Size

- 69% clinical cure rate for linezolid
- Actual CE population = 94 patients
- 59 patients minocycline+rifampicin,
  35 patients linezolid
- Power = 0.75

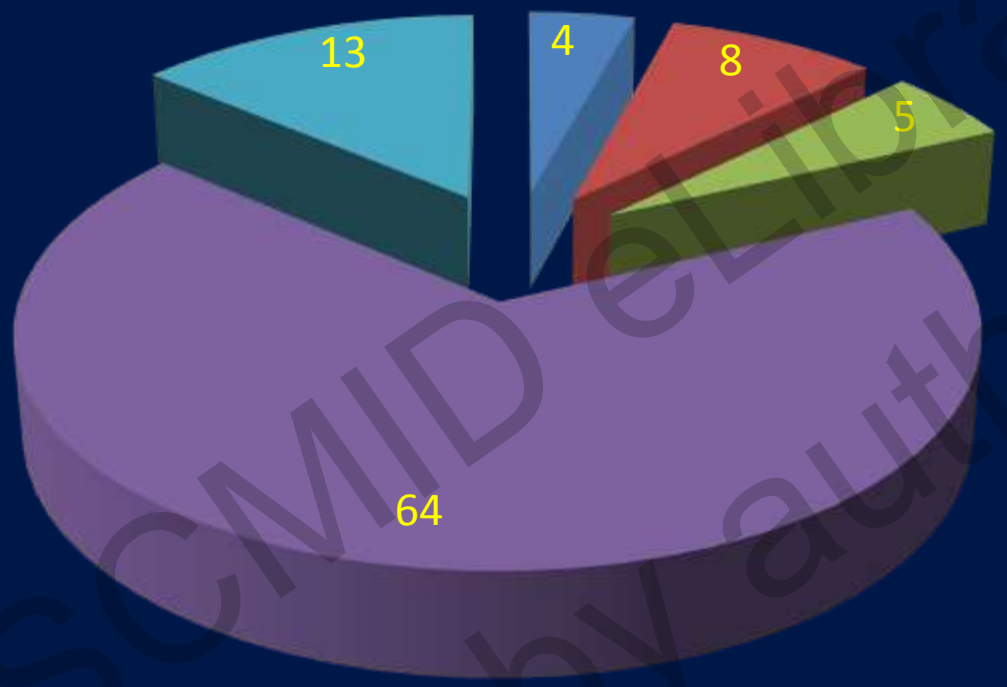
Patient Disposition



Demographics

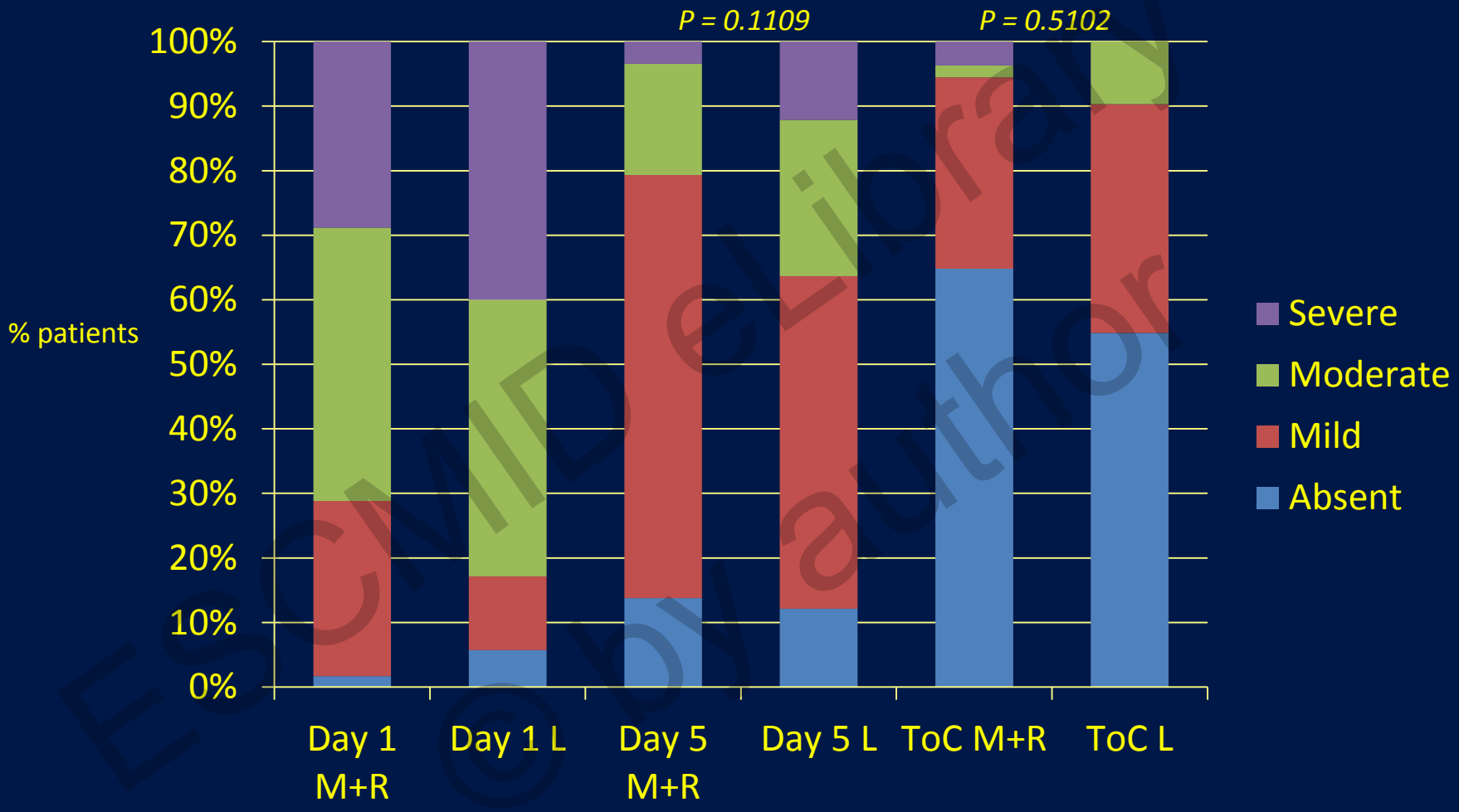
	Minocycline Rifampicin N:59	Linezolid N:35	Total N:94
Patient Sex			
n	59	35	94
Female	29 (49.2%)	15 (42.9%)	44 (46.8%)
Male	30 (50.8%)	20 (57.1%)	50 (53.2%)
Patient Age (years)			
n	59	35	94
Mean	70.8	72.7	71.5
SD	15.31	16.45	15.68
Median	75.0	78.0	75.0
Min-Max	37.0 to 93.0	39.0 to 95.0	37.0 to 95.0
Age Groups			
n	59	35	94
25 to 49	8 (13.6%)	4 (11.4%)	12 (12.8%)
50 to 64	9 (15.3%)	6 (17.1%)	15 (16.0%)
65 to 79	22 (37.3%)	11 (31.4%)	33 (35.1%)
80 and Over	20 (33.9%)	14 (40.0%)	34 (36.2%)
Patient BMI (kg/m²)			
n	59	35	94
Mean	26.0	25.5	25.8
SD	5.90	5.69	5.80
Median	24.8	24.8	24.8
Min-Max	17.3 to 48.9	18.7 to 49.8	17.3 to 49.8

Main type of Infection



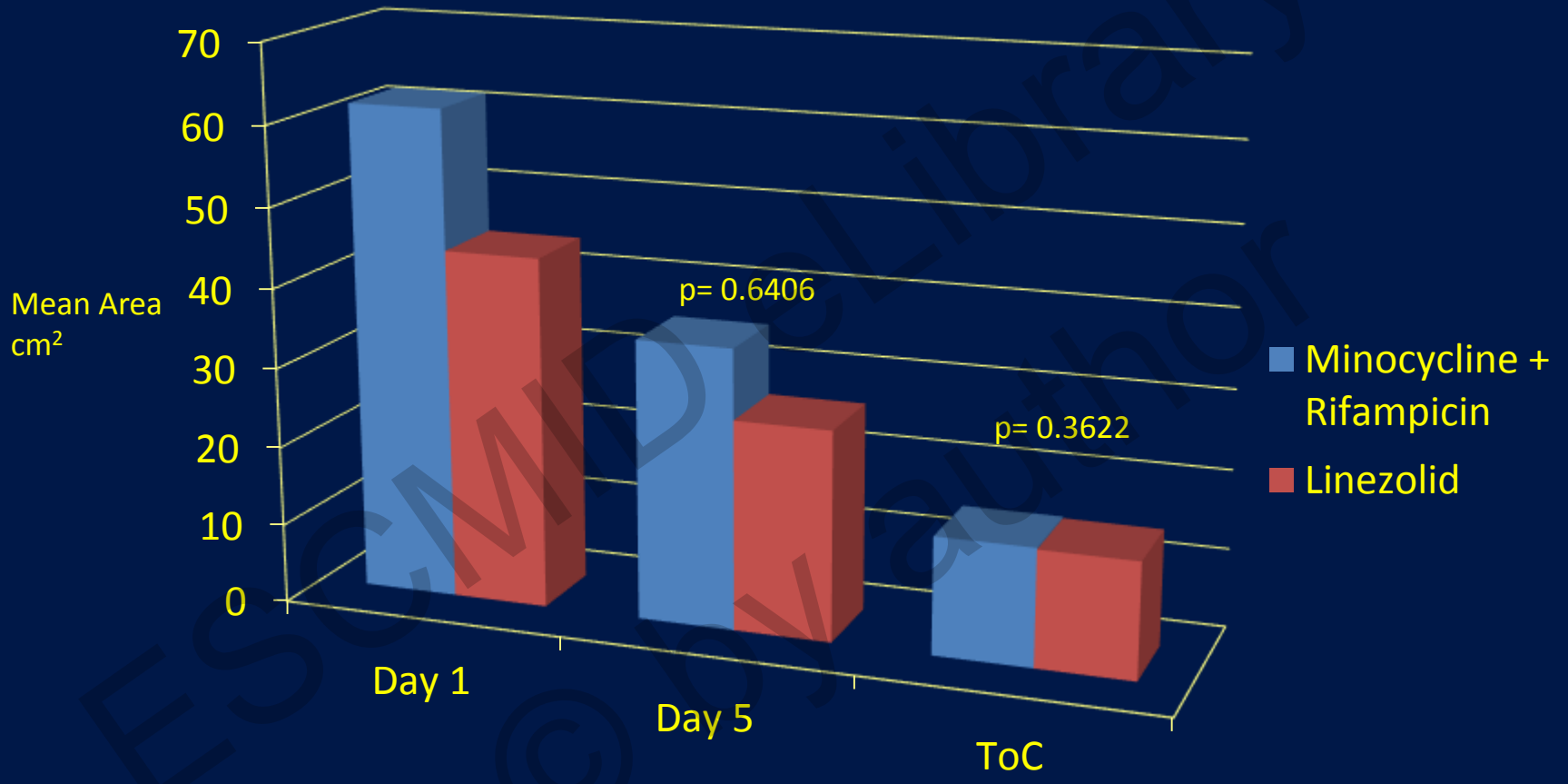
CE population n=94

Erythema



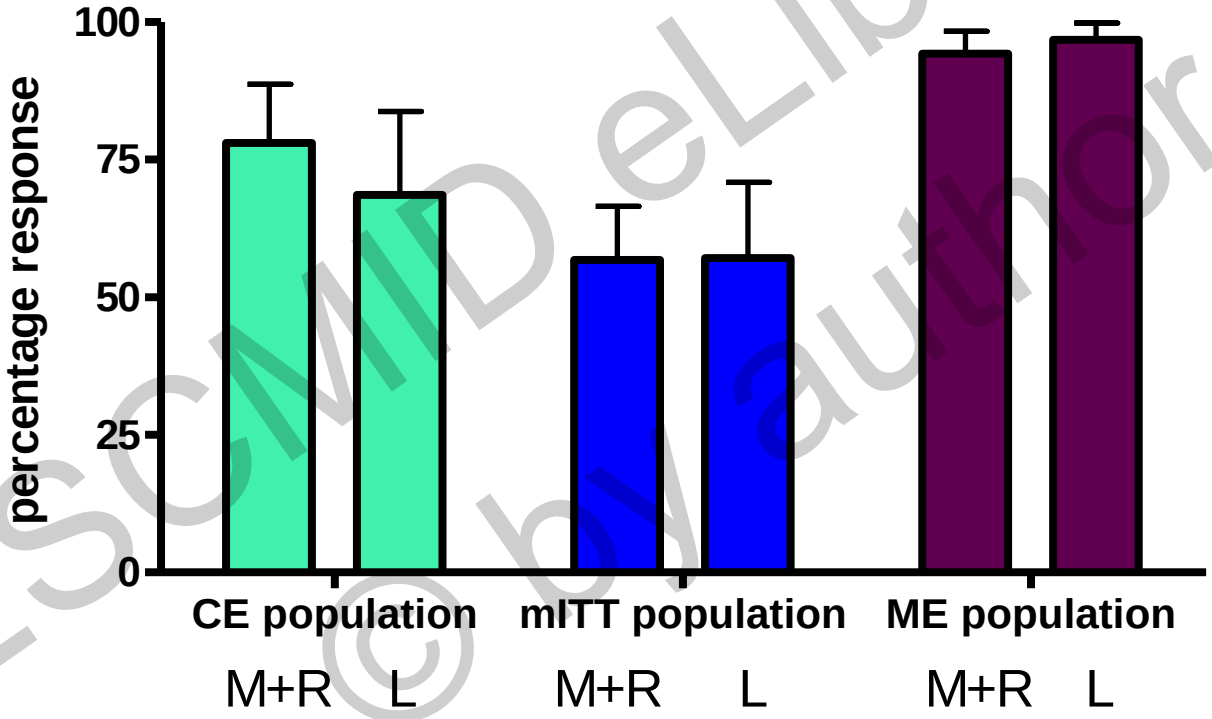
Statistical comparison Cochran Mantel Haenszel Test (CMH)

Area of infection (cm^2)



Statistical comparison Wilcoxon Test

Figure. Response rates to minocycline plus rifampicin (M+R) or linezolid (L) in the clinically evaluable (CE), modified intention to treat (mITT) and microbiologically evaluable (ME) populations



Adverse Events

- 31 patients (38.3%) in minocycline+rifampicin arm reported an adverse event
- 20 patients (47.6%) in linezolid arm reported an adverse event
- Difference was not statistically significant
- 15pts (18.5%) died in the minocycline+rifampicin arm, 7(16.7%) in the linezolid arm. No deaths were related to therapy

MIC distribution of Study MRSA

Minocycline MIC (mg/L)	Number	
0.06	0	
0.12	58	
0.25	14	
0.5	18	
1	11	← Minocycline breakpoint
2	17	
4	0	← Minocycline plus rifampicin breakpoint
8	1	
16	3	
≥32.0	0	

Conclusions – Clinical Trial

- Also see paper poster P2117
  - minocycline plus rifampicin is non-inferior to linezolid in the treatment of cSSSI due to MRSA with cure rate of 78% and 68.6% respectively.
  - Adverse events were higher in the linezolid arm (47.6%) then minocycline plus rifampicin (38.3%).

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