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Joint Polymyxin Working Group

Working Group/Contributors

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Testing Methods

Reference testing is the ISO-standard broth microdilution method, using

a. cation-adjusted Mueller-Hinton Broth, with

b. no additives in any part of the testing process (in particular, no polysorbate-80 or other surfactants);

c. trays must be made of plain polystyrene and not otherwise treated before use, and

d. sulfate salts of polymyxins must be used (in particular, the methanesulfonate derivative of colistin must not be used)

Disk diffusion and gradient diffusion testing require further studies to improve or confirm their correlation with reference method testing. Agar dilution needs work done.

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Colistin

Most of the way there…

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Protein Binding

- Previous estimates were incorrect as the adherence to plastics compromised the assay
- Now repeated using two independent methods: ultracentrifugation and rapid equilibrium dialysis in Teflon® cells, the protein binding of colistin was shown to be concentration-independent over the observable range of concentrations found in mice and humans
- Binding compared between healthy human plasma and critically ill patients

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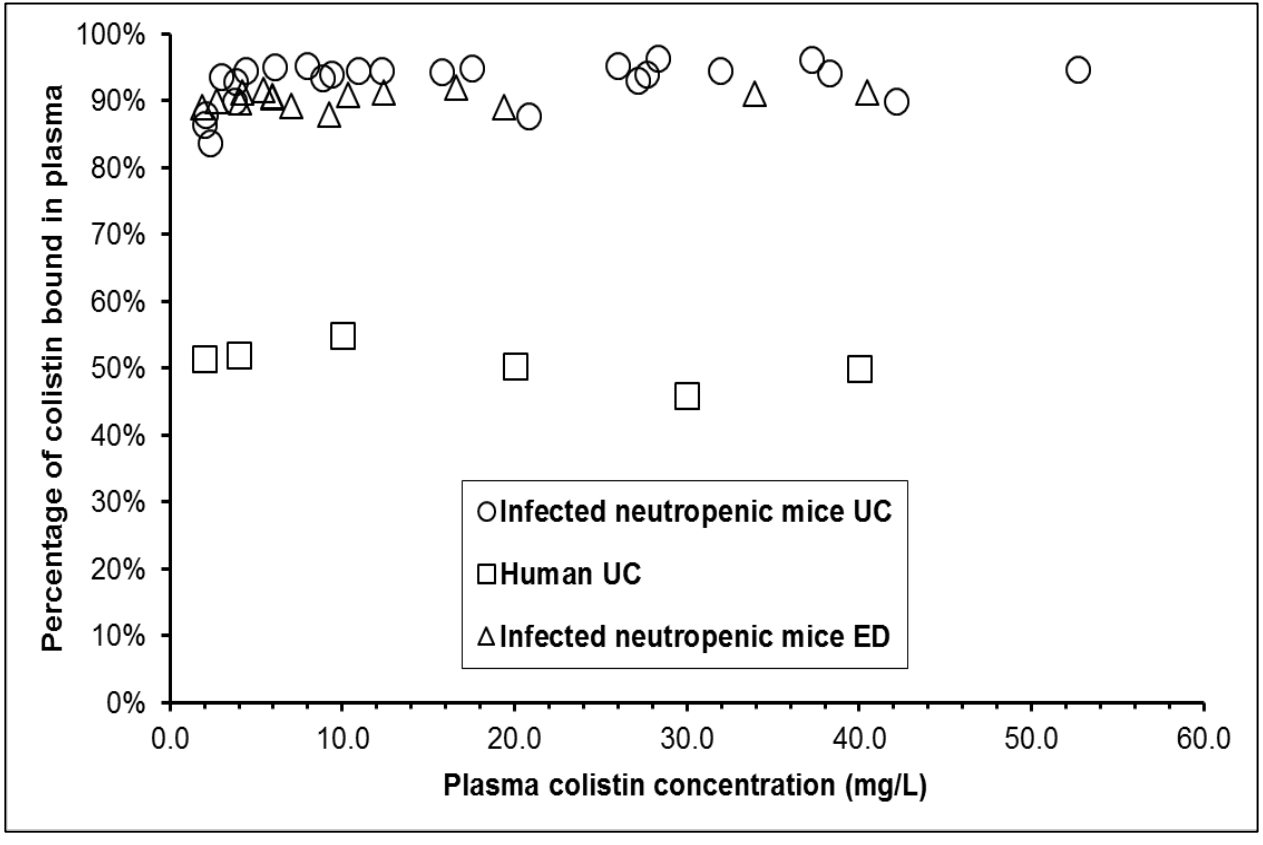
Protein Binding



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Protein Binding

	Unbound fraction in plasma (fu)	
	Critically-ill patients	*Healthy human plasma*
Number[a]	66	11
Average	0.49	0.48
SD	0.11	0.06
10th percentile	0.36	0.41
25th percentile	0.42	0.42
50th percentile (Median)	0.48	0.47
75th percentile	0.56	0.51
90th percentile	0.63	0.59

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Pharmacodynamic Animal Model Studies

Model	Species/Strain	Target value of colistin *f*AUC/MIC		
		Stasis	1-$\log_{10}$ kill	2-$\log_{10}$ kill
Thigh Infection	*P. aeruginosa*	Means 7.5	9.2	11.5 .
	ATCC 27853	9.94	12.4	15.8
	PAO1	6.01	6.53	7.34
	19056	6.41	8.56	11.3
	A. baumannii	Means 5.0	7.8	11.4 .
	ATCC 19606	1.47	3.45	9.13
	248-01-C.248	3.91	6.11	7.44
	N-16870.213	9.47	13.9	17.6

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Pharmacodynamic Animal Model Studies

	P. aeruginosa	Means 29.3	48.7	78.4 . .
	ATCC 27853	34.1	43.3	51.8
	PAO1	15.2	44.8	[a]
Lung	19056	38.6	57.9	105
Infection	*A. baumannii*			
	ATCC 19606	[b]	[b]	[b]
	248-01-C.248	11.6	20.8	36.8
	N-16870.213	[b]	[b]	[b]

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Target Attainment Rates – Analysis of Data from a Prospective Clinical Study

Multi-national (USA, Greece, Thailand) multi-centre study focussing on the PK/PD of colistin (administered intravenously as colistin methanesulfonate (CMS)) in critically-ill patients with multi-resistant Gram-negative infections, funded by the NIH (https://clinicaltrials.gov/ct2/show/NCT00235690)

TABLE 3 Renal Function Groups

Group	N	CLcr (uncorrected) range in mL/min
1	27	5.4 – 26.9
2	27	27.0 – 40.7
3	27	41.6 – 57.0
4	27	57.8 – 76.0
5	27	77.2 – 117.3
6	27	121.1 – 211.2

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Target Attainment Rates – Analysis of Data from a Prospective Clinical Study

Target attainment rates in each of the 6 renal function categories were determined with the following parameters:

- Plasma protein binding in critically-ill patients and healthy humans of ~50% (i.e. fu of ~0.5)
- A target *f*AUC24/MIC of 12 (the approximate mean 2-log kill target for P. *aeruginosa* and *A. baumannii* in mouse thigh infection and the approximate highest 1-log kill target for the three strains of each species in the same infection model corresponds to a $fC_{ss,avg}$/MIC of 0.5. This corresponds to a $C_{ss,avg}$/MIC of 1 (plasma protein binding of ~50%).

Thus, with these parameters, the target attainment rate at each MIC is equivalent to the target attainment rate for $C_{ss,avg}$ (i.e. for **total** colistin)

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Target Attainment Rates – Analysis of Data from a Prospective Clinical Study

TABLE 4: Current FDA and EMA dosing recommendations according to creatinine clearance

Renal Function Group (mL/min)	FDA Daily dose[a]	EMA Daily dose[a]
≥ 80	2.5 – 5 mg/kg	300 mg[b]
50 – <80	2.5 – 3.8 mg/kg	300 mg
30 – <50	2.5 mg/kg	183 – 250 mg
10 – <30	1 mg/kg	150 – 183 mg
<10	Not stated	117 mg

[a] mg of colistin base activity

[b] doses up to 400 mg may be required in patients with good renal function although there is limited experience with these doses

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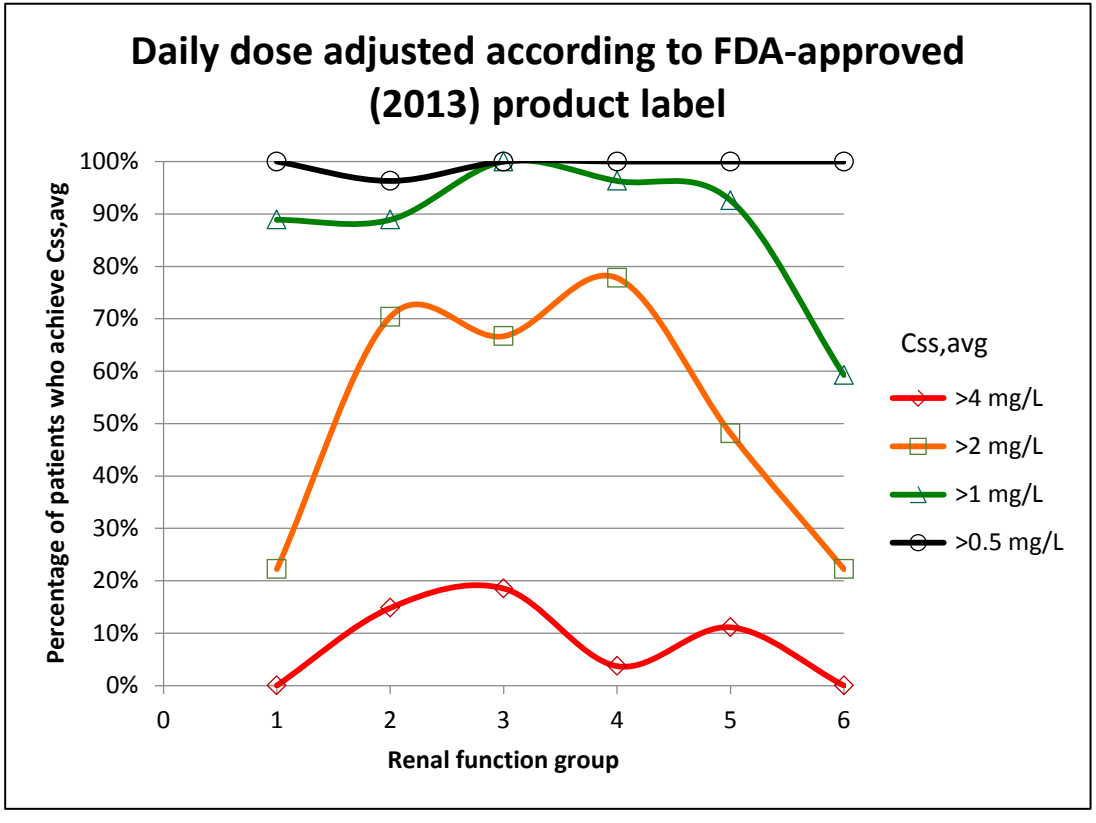
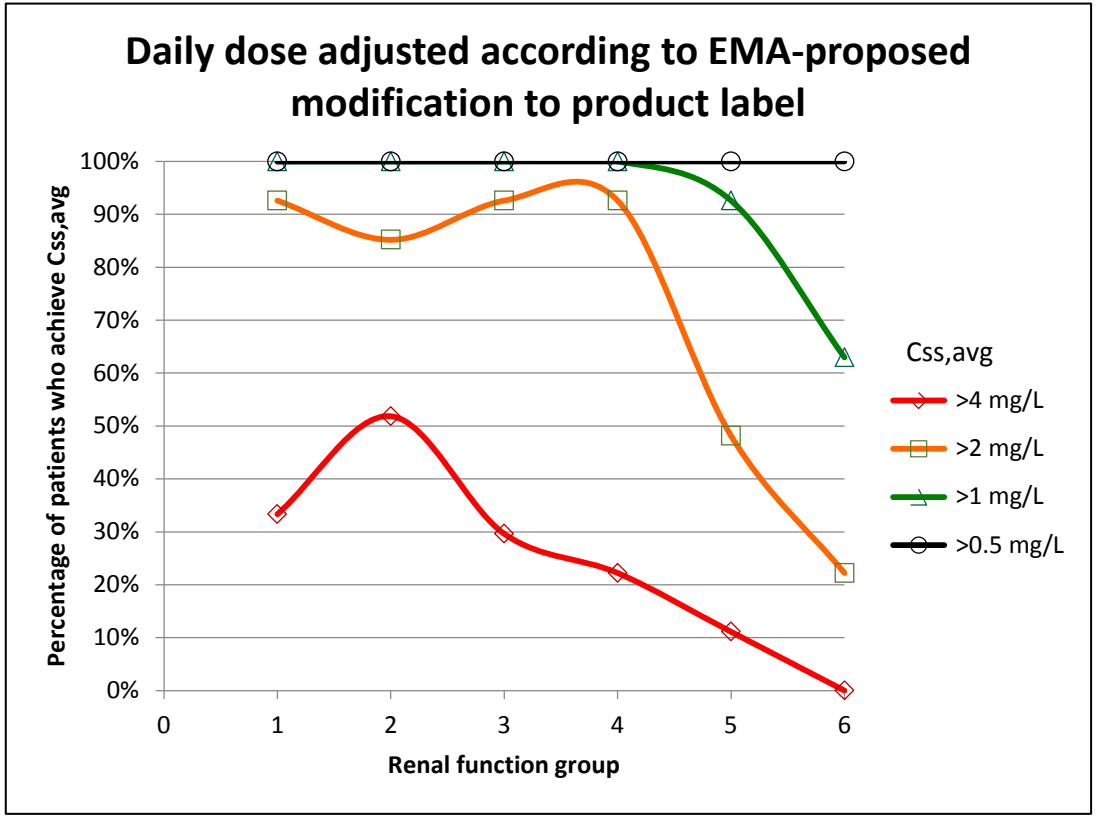
Target Attainment Rates – Analysis of Data from a Prospective Clinical Study



Target Attainment Rates – Analysis of Data from a Prospective Clinical Study



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Breakpoint Proposal

If it is agreed that:

- The target *f*AUC$_{24}$/MIC ratio of 9 and 12 for a 1-log and 2-log kill in mouse thigh infection is most appropriate to the types of patients who are likely to be treated with colistin (except VAP; see below about lung infection model), and
- This approach to target attainment is as valid as the population PK/Monte Carlo simulation approach, and
- That the variance in protein binding is sufficiently small that is can be safely be ignored, and
- A target attainment rate of ≥ 90% is sufficient, which only achieved with EMA dosing recommendations

Then the **breakpoint could be 2 mg/L**, and only if patients with creatinine clearances of >75 mL/min are given the highest possible doses (>300 mg colistin base activity per day), noting that even in these patients, 90% TA was not achieved even with 350 mg (FDA) or 360 mg (EMA) of CBA per day.

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Colistin: MIC distributions

ECOFF

Species (sources)	0.03	0.06	0.13	0.25	0.5	1	2	4	8	16	32	64	128
A. baumannii (8)			1	55	117	55	12	1	6	1	2	1	
E. aerogenes (7)		4	4	41	102	41	11	2	3	3			4
E. cloacae (7)		30	19	170	366	172	54	17	40	80	23	2	21
E. coli (10)		243	255	2064	3074	773	143	21	13	52	7	1	30
K. oxytoca (7)		16	9	103	316	149	21	6	1	10	2		2
K. pneumoniae (8)		50	33	345	754	439	124	19	11	35	13	1	9
P. aeruginosa (12)	1	5	18	99	917	1786	1160	131	29	46	6	1	12

Source: http://mic.eucast.org Dec 6, 2014

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Unresolved Issues

1. The current FDA dosing recommendations do not perform as well in terms of target attainment as the EMA recommendations in this analysis.
2. Based on the mouse lung infection model, the very high *f*AUC_{24}/MIC ratios required even for stasis appear unachievable with current dosing recommendations. Even for stasis with *P. aeruginosa*, the target *f*AUC_{24}/MIC is more than double the value used for the target attainment rate estimations used above.
3. We don't yet know that the target *f*AUC_{24}/MIC values for Enterobacteriaceae. We don't believe we can assume that it will be the same as for the two non-fermenter species in this analysis.
4. We don't have equivalent information for polymyxin B to make the same estimates of target attainment rates. It is not safe to assume that they will be equivalent to colistin [Nation et al., Clin Infect Dis. (2014) 59 (1): 88-94]