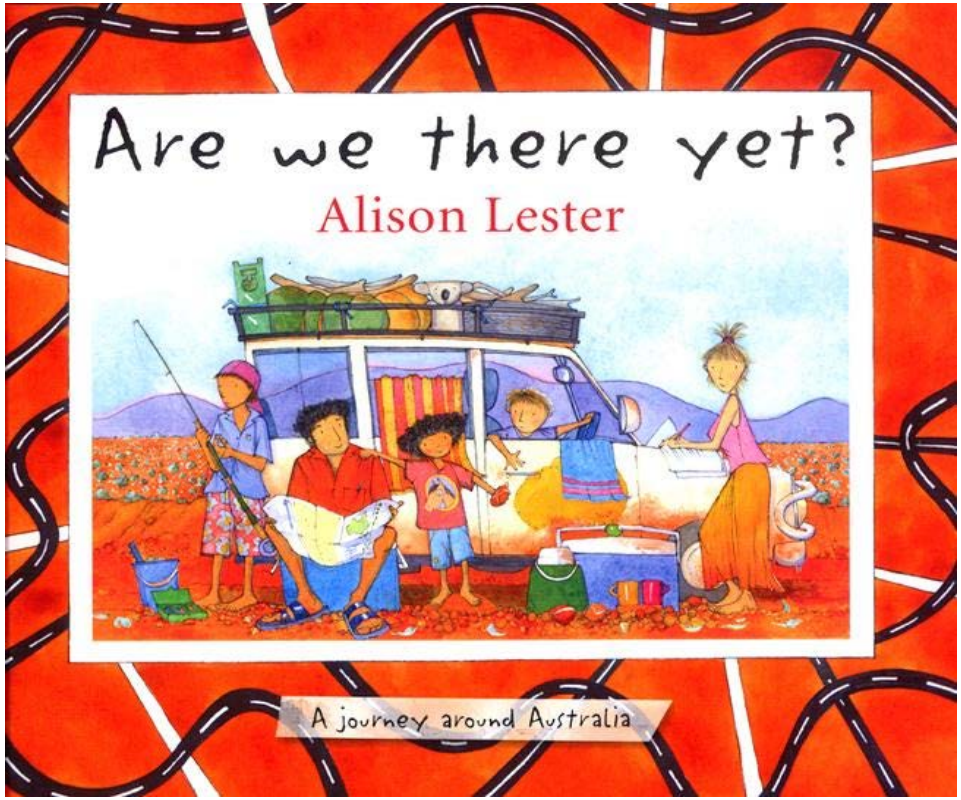
CLINICAL AND LABORATORY STANDARDS INSTITUTE

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

Joint Polymyxin Working Group



MIC measurement

- Polymyxins bind to plastics and other laboratory materials
  - Due to electrostatic interaction (polymyxins are polycationic in solution)
  - Concentration dependent – lower binding at higher concentrations
- Polymyxins are mixtures of two major components (A & B, B1 & B2)
  - The ratios can vary – available evidence suggests similar potencies
  - **Q1:** Are we agreed that we can ignore this variation?
- Reference method:
  - Now agreed to be BMD in Mueller-Hinton with no polysorbate-80
    - P-80 acts synergistically with polymyxins, so "falsely" lowers the MICs
  - For colistin, the test reagent is colistin sulphate (not methanesulfonate)
  - Reproducibility established in previously presented QC studies
  - **Q2:** Should we specify that the trays should be made of polystyrene?

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Colistin

The story so far…

Colistin: MIC distributions

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

Clear All

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P. aeruginosa: Colistin ECV/ECOFF

Step 1. Population Data | *P. aeruginosa* | Colistin

MIC	Log_2MIC	Raw Count	Cum. Count	Fitted
0.001	-10		0	0.0
0.002	-9		0	0.0
0.004	-8		0	0.0
0.008	-7		0	0.0
0.016	-6		0	0.0
0.03	-5	1	1	0.0
0.06	-4	5	6	0.1
0.125	-3	18	24	5.1
0.25	-2	99	123	127.1
0.5	-1	917	1040	892.7
1	0	1786	2826	1823.7
2	1	1160	3986	1097.9
4	2	131	4117	193.0
8	3	29	4146	9.6
16	4	46	4192	0.1
32	5	6	4198	0.0
64	6	1	4199	0.0
128	7	12	4211	0.0
256	8		4211	
512	9		4211	
1024	10		4211	

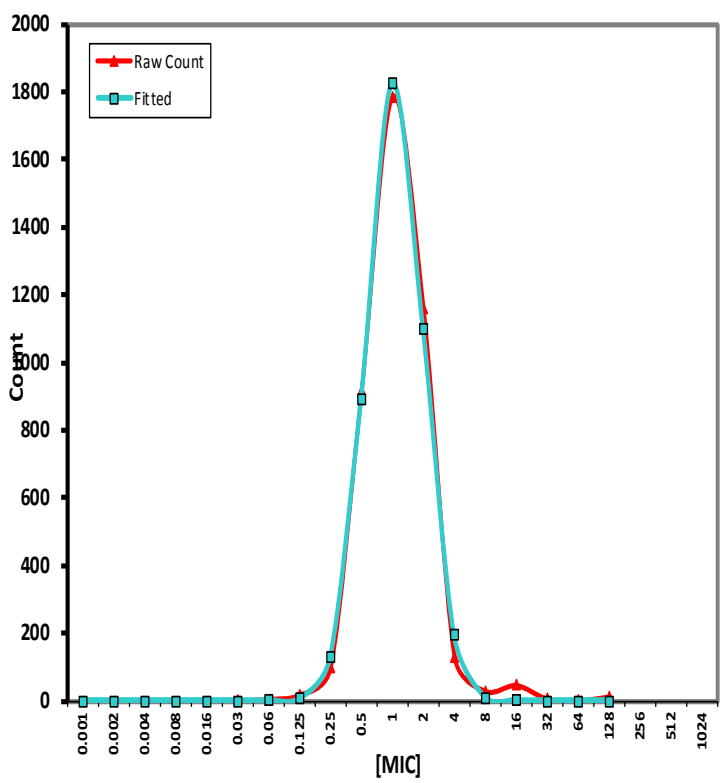
Enter/paste data in this column

Modal MIC	1	
Log_2MIC Mode	0	
Max Log_2MIC	7	
Selected Log2 Mean	-0.42	=0.75
Selected Log2 SD	0.855	

Selected CO_{WT} Values		%>
CO_{WT} 95.0%	2	5.3%
CO_{WT} 97.5%	4	2.2%
CO_{WT} 99.0%	4	2.2%
CO_{WT} 99.9%	8	1.5%

Clear All

REVIEW AREA



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E. cloacae: Colistin ECV/ECOFF

Step 1. Population Data | *E. cloacae* | Colistin

MIC	Log_2MIC	Raw Count	Cum. Count	Fitted
0.001	-10		0	0.0
0.002	-9		0	0.0
0.004	-8		0	0.0
0.008	-7		0	0.0
0.016	-6		0	0.0
0.03	-5		0	0.0
0.06	-4	30	30	2.0
0.125	-3	19	49	35.0
0.25	-2	170	219	193.9
0.5	-1	366	585	343.0
1	0	172	757	195.2
2	1	54	811	35.5
4	2	17	828	2.0
8	3	40	868	0.0
16	4	80	948	0.0
32	5	23	971	0.0
64	6	2	973	0.0
128	7	21	994	0.0
256	8		994	0.0
512	9	2	996	0.0
1024	10		996	

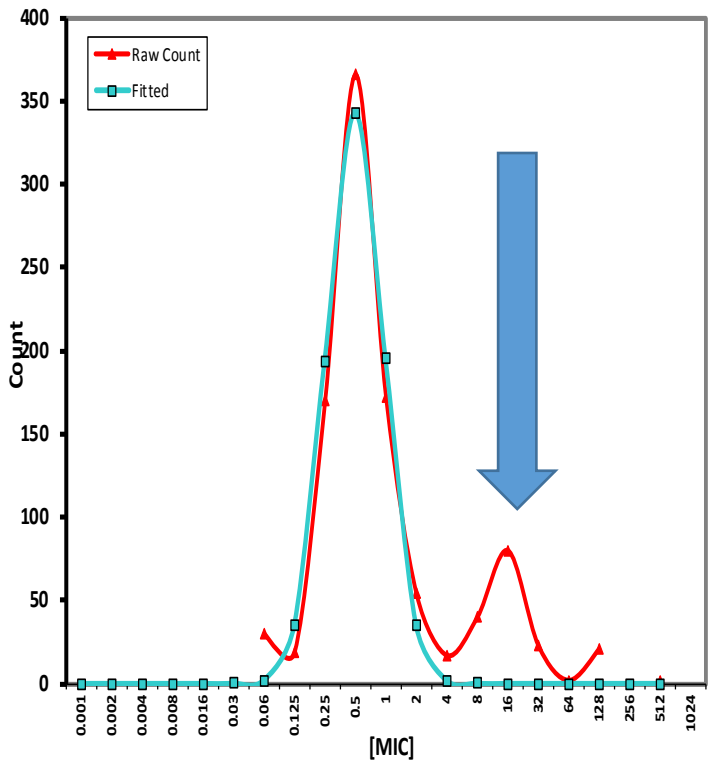
Enter/paste data in this column

Clear All

Modal MIC	0.5	
Log_2MIC Mode	-1	
Max Log_2MIC	9	
Selected Log2 Mean	-1.5	=0.35
Selected Log2 SD	0.891	

Selected CO_{WT} Values		%>
CO_{WT} 95.0%	1	24.0%
CO_{WT} 97.5%	2	18.6%
CO_{WT} 99.0%	2	18.6%
CO_{WT} 99.9%	4	16.9%

REVIEW AREA



Colistin ECVs/ECOFFs

Species	Calculated ECV (mg/L)	EUCAST 'eyeball' ECV (mg/L)
A. baumannii	2	2
E. aerogenes	1	2
E. cloacae	2	2
E. coli	1	2
K. oxytoca	2	2
K. pneumoniae	2	2
P. aeruginosa	4	4

Q3: Which ECVs/ECOFFs should we go with?

Other Susceptibility Testing Methods

- Agar dilution – may be acceptable, needs further work
  - Gales et al., JCM 2001 (only 35 isolates)
- Disk diffusion – poor correlation
  - Gales et al., JCM 2001
  - Van der Heijden et al., ACMA 2007
- Gradient diffusion – poor correlation
  - Van der Heijden et al., ACMA 2007

- **Q4:** Can we confirm that BMD is the only currently acceptable method?

In vitro pharmacodynamics

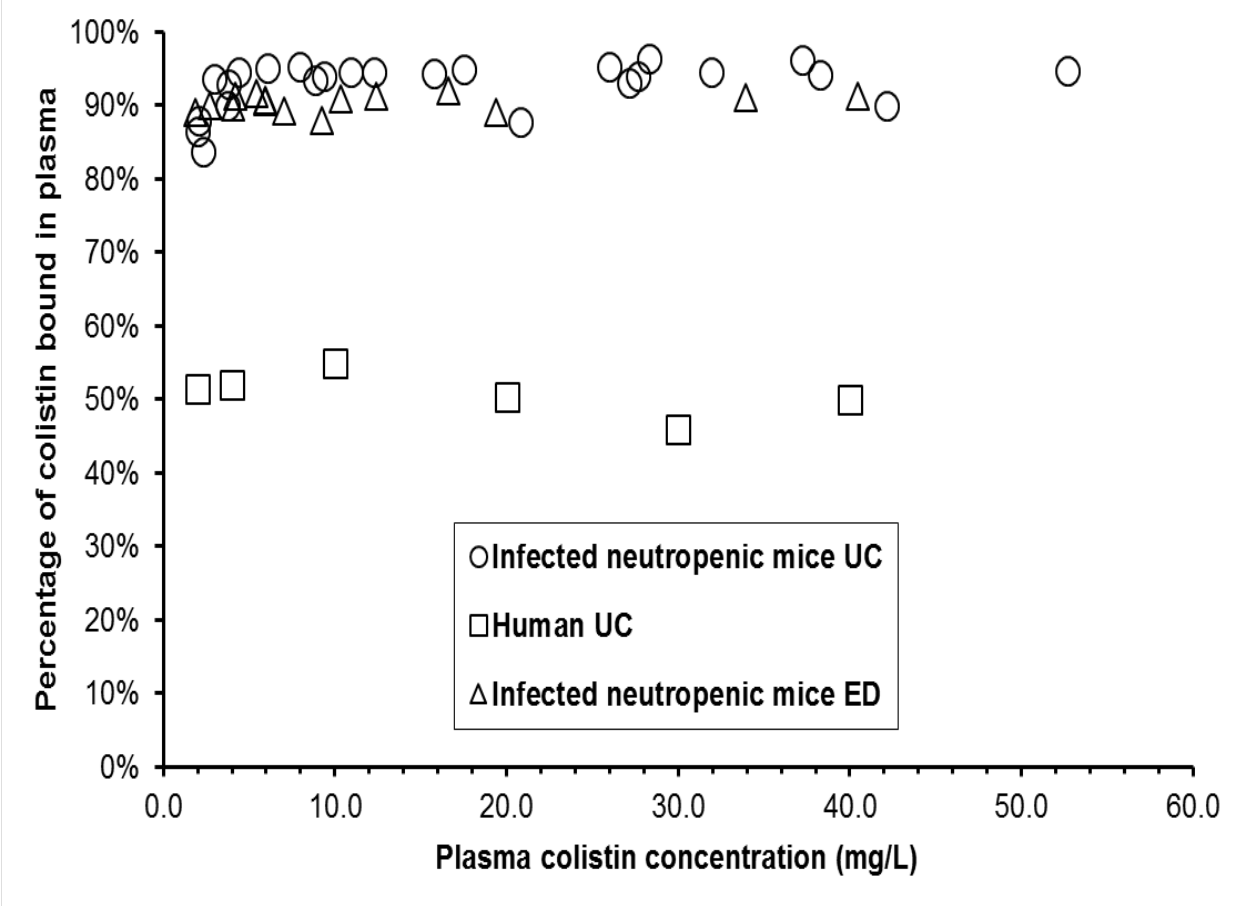
- Concentration-dependent killing
  - Li et al., AAC 2001, 45(3):781
- Short postantibiotic effect
  - Li et al., AAC 2001, 45(3):781
- Hetero-resistance common in some species
  - *A. baumannii*
    - Tan et al., AAC 2007
    - Owen et al., JAC 2007
  - *K. pneumoniae*
    - Poudyal et al., JAC 2008
  - *Enterobacter* spp.
    - Bell et al., ICAAC 2011

Protein Binding

- Original work suggested concentration-dependent binding
  - subsequently shown to be an artefact of the assay method
- By ultracentrifugation and rapid equilibrium dialysis in Teflon® cells there is no concentration dependence
  - Mouse ~90%
  - Humans ~50%

Nation, 2014 personal communication

Protein Binding



Nation, 2014 personal communication

Protein Binding

- Almost the same in critically ill as healthy, although larger variance

	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

Nation, 2014 personal communication

Mouse thigh and lung PK/PD data

Model	Species/Strain	Target value of colistin *f*AUC/MIC		
		Stasis	1-$\log_{10}$ kill	2-$\log_{10}$ kill
Thigh Infection	*P. aeruginosa*			
	ATCC 27853	9.94	12.4	15.8
	PAO1	6.01	6.53	7.34
	19056	6.41	8.56	11.3
	A. baumannii			
	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

Cheah et al, 2014 submitted

Mouse thigh and lung PK/PD data

	P. aeruginosa			
	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

Cheah et al, 2014 submitted

Pharmacokinetics

	Healthy volunteer		Critically ill patients					
	Couet *et al.* (22)		Plachouras *et al.* [17]		Garonzik *et al.* [19]		Gregoire *et al.* (Grégoire *et al.*, 21st ECCMID, 2011, 804pp.)	
	Typical value	IIV (CV%)	Typical value	IIV (CV%)	Typical value	IIV (CV%)	Typical value	IIV (CV%)
CMS								
CL (mL/min)	148 (5)	15 (47)	228 (10)	37 (15)	61.0 (–) 154.3[a]	–	107 (–)	42 (30)
V_c (L)	8.92 (6)		13.5 (45)		11.5 (5)	32	5.3 (10)	
Q (mL/min)	41.4 (15)		2217 (35)		133 (12)	84	123 (13)	
V_p (L)	5.1 (–)		28.9 (22)		18.7 (9)	79	29.7 (12)	
CL_R (mL/min)	103 (8)	16 (48)	–		29.3 (9) 122.6[a]	–	82.8 (10)	
Colistin								
CL/f_m (mL/min)	48.7 (15)		151.5[b] (19)	59 (36)	45.3 (–) 65.9[a]	23	33.4 (–)	
V/f_m (L)	12.4 (15)	19 (53)	189[b] (12)		45.1 (6)	48	7.2 (11)	
CL_R/f_m (mL/min)	1.9 (19)	56 (49)			7.0 29.4[a]		2.1 (17)	63 (50)

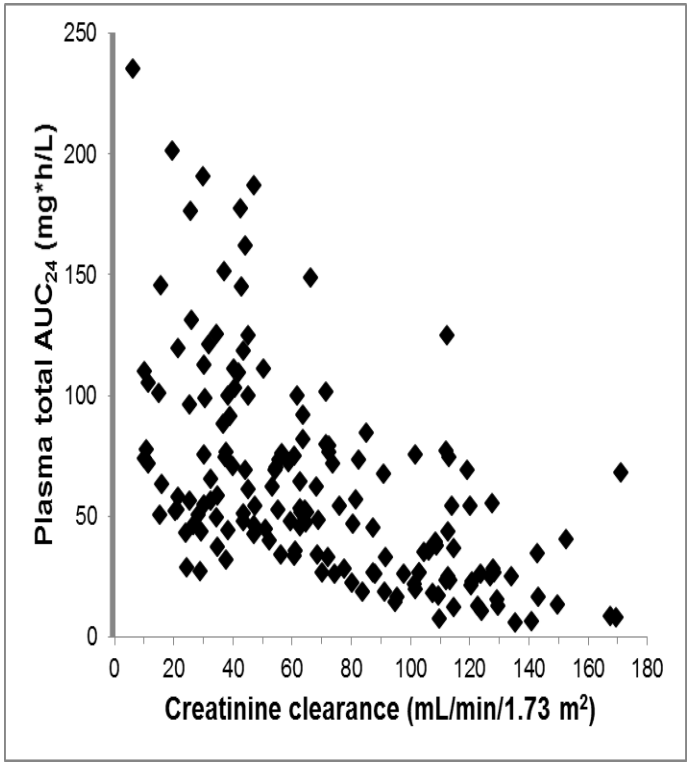
CL, clearance of CMS; CL/f_m, clearance of formed colistin; CL_R, renal clearance of CMS; CL_R/f_m, renal clearance of formed colistin; CV, coefficient of variation; IIV, inter-individual variability; Q, intercompartmental clearance for CMS; V_c, volume of distribution of central compartment for CMS; V/f_m, volume of distribution of formed colistin; V_p, volume of distribution of peripheral compartment for CMS.

[a]Parameter value calculated from the authors' formula for a creatinine clearance of 120 mL/min/1.73 m^2.

[b]CL/f_{coli} and V/f_{coli} are reported instead of CL/f_m and V/f_m.

Pharmacokinetics

- Multi-center study R01 AI070896 NIAID-funded study in critically ill patients
- AUC_{24} greatly influenced by renal function



Approved dosing regimens

- Coly-Mycin M® FDA Product Information

TABLE 1. Suggested Modification of Dosage Schedules of Coly-Mycin M Parenteral for Adults with Impaired Renal Function

Renal Function	Degree of Impairment			
	Normal	Mild	Moderate	Considerable
Plasma creatinine, mg/100 mL	0.7–1.2	1.3–1.5	1.6–2.5	2.6–4.0
Urea clearance,% of normal	80–100	40–70	25–40	10–25
Dosage				
Unit dose of Coly-Mycin M, mg	100–150	75–115	66–150	100–150
Frequency, times/day	4 to 2	2	2 or 1	every 36 hr
Total daily dose, mg	300	150–230	133–150	100
Approximate daily dose, mg/kg/day	5.0	2.5–3.8	2.5	1.5

Note: The suggested unit dose is 2.5–5 mg/kg; however, the time INTERVAL between injections should be increased in the presence of impaired renal function.

Monte Carlo Simulations

- For total daily doses of 150mg and 300mg colistin base activity
- Assumptions used (patients with CrCl >80 mL/min/1.73m^2)
  - Clearance in normally distributed
  - Protein binding is normally distributed
- Values selected for multi-center study R01 AI070896 NIAID-funded study in critically ill patients
  - Apparent clearance of formed colistin (L/h): Mean of 10.1 ± 5.8
  - Protein binding (%): Mean of 51 ± 11
- Monte Carlo Simulation: Crystal Ball® v11.1.2.3: n=5000 trials
- Targets values: the highest for each species in each mouse model

Monte Carlo Simulations

Thigh infection model % target attainment **Daily dose on 300mg CBA**

MIC	*P. aeruginosa* Stasis	*eruginosa* kill	*aumannii* sis	*A. baumannii* 1-log kill
0.25	100		00	100
0.5	100		100	100
1	100		100	100
2	99.9		0	79.5
4	4.7	.1	9.0	0
8	0	0	0	0

PROBLEM!

DOES NOT TALLY WITH OBSERVATIONS FROM THE CLINICAL STUDY

MORE WORK REQUIRED!!!!!

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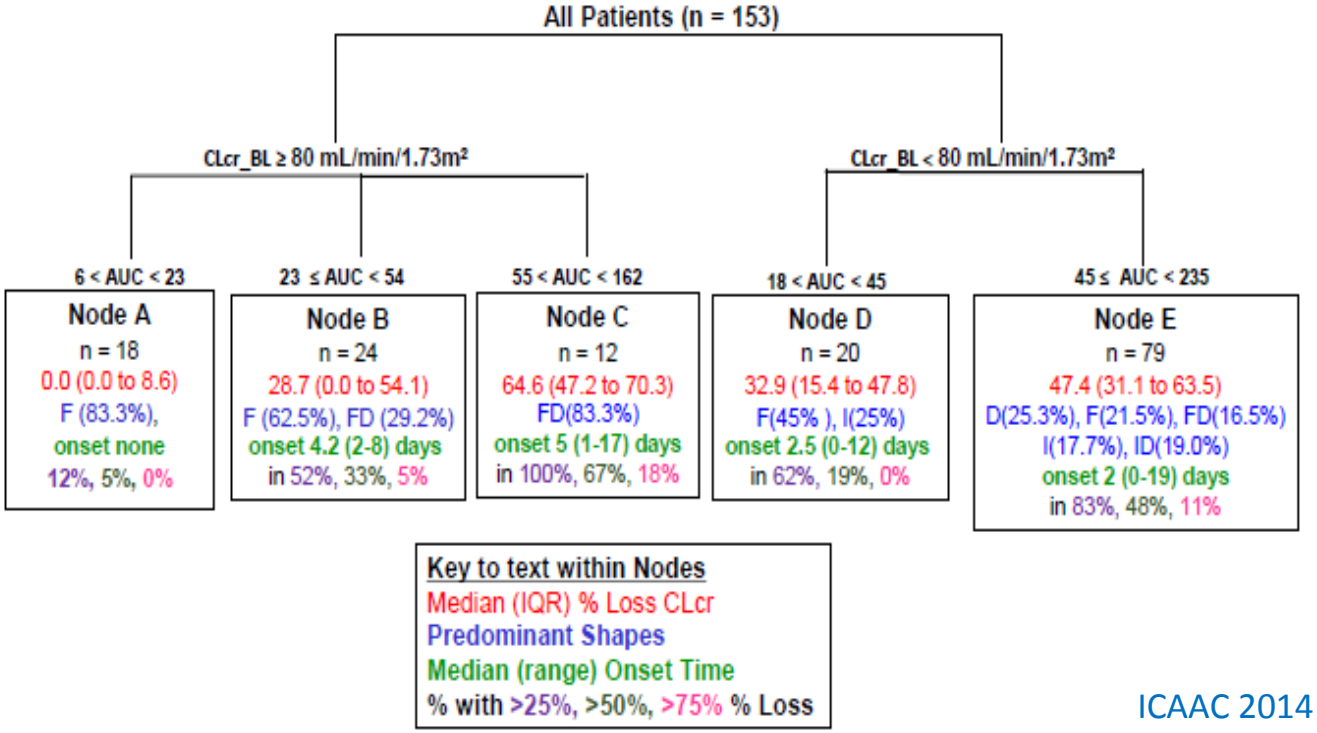
Toxicodynamics (TD) for Colistin-Associated Changes in Creatinine Clearance (CLcr)

ALAN FORREST[1]*, FERNANDA P. SILVEIRA[2], VISANU THAMALIKHITKUL[3], SAMIRA M. GARONZIK[1], KONSTANTINOS MANDRAGOS[4], SHMUEL SHOHAM[5], DAVID L. PATERSON[6], JIAN LI[7], ROGER L. NATION[7]

[1] SUNY School of Pharmacy, Buffalo, NY; [2] Univ Pittsburgh, PA; [3] Mahidol Univ, Bangkok Thailand; [4] Korgialeneion Benkeion Hosp, Athens, Greece; [5] Washington Hosp Center, Washington DC; [6] Univ Queensland, Brisbane, Australia; [7] Monash Institute of Pharmaceutical Sciences, Melbourne, Australia

Figure 2: Tree-Based Model Relating CLcr % Loss to Drug Exposure & Covariates



ICAAC 2014 Poster A-038A

Summary of Progress

- Susceptibility testing
  - Reference method confirmed for both agents
  - Comparability of agar dilution needs to be explored
- Animal model pharmacodynamics
  - Now established for colistin in mouse thigh and lung models
    - For *P. aeruginosa* and *A. baumannii* only so far
    - Tentative pharmacodynamic cutoffs can be set once approach to MCS has been resolved
  - Insufficient information on polymyxin B so far
- Human clinical data
  - Many “noisy” single center clinical studies
  - Only one true PK/PD-focused study (multi-center NIAID funded) and clinical outcome data are still undergoing analysis, and only for colistin (methanesulfonate)

For a vote

- **Q1:** Are we agreed that we can ignore component variation?
- **Q2:** Should we specify that the MIC trays should be made of polystyrene?
- **Q3:** Which ECVs/ECOFFs should we go with – calculated vs eyeball?
- **Q4:** Can we confirm that testing is BMD only at this point?