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Next-generation clinical breakpoints: infection site, dosing and administration

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Topics

- Breakpoint tables in 2018 - aspects on infection site, dosing size, and mode of administration
- Urinary tract infections – what could in theory be achieved?
- Systemic infections – what could in theory be achieved?
- Novel antimicrobials and selection of dosing regimen
- Can we trust the MICs?
- The cristal ball: what will breakpoint tables look like in the future?

Breakpoint tables in 2018

Indication-specific breakpoints – urinary tract

Enterobacteriaceae (new taxonomy: Enterobacterales*)

EUCAST Clinical Breakpoint Tables v. 8.0, valid from 2018-01-01

Cephalosporins ¹	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes
	S ≤	R >		S ≥	R <	
Cefaclor	-	-	-	-	-	<p>1. The cephalosporin breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including ESBL and plasmid mediated AmpC). Some isolates that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as tested, i.e. the presence or absence of an ESBL does not in itself influence the categorisation of susceptibility. ESBL detection and characterisation are recommended for public health and infection control purposes.</p> <p>2. The cefoxitin ECOFF (8 mg/L) has a high sensitivity but poor specificity for identification of AmpC-producing Enterobacteriaceae as this agent is also affected by permeability alterations and some carbapenemases. Classical non-AmpC producers are wild type, whereas plasmid AmpC producers or chromosomal AmpC hyperproducers are non-wild type.</p> <p>3. For susceptibility testing purposes, the concentration of avibactam is fixed at 4 mg/L.</p> <p>4. For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L.</p> <p>5. Breakpoints are based on high dose therapy, see table of dosages (1.5 g x 3).</p>
Cefadroxil (uncomplicated UTI only)	16	16	30	12	12	
Cefalexin (uncomplicated UTI only)	16	16	30	14	14	
Cefazolin	-	-	-	-	-	
Cefepime	1	4	30	27	24	
Cefixime (uncomplicated UTI only)	1	1	5	17	17	
Cefotaxime	1	2	5	20	17	
Cefoxitin (screen) ²	NA	NA	30	19	19	
Cefpodoxime (uncomplicated UTI only)	1	1	10	21	21	
Ceftaroline	0.5	0.5	5	23	23	
Ceftazidime	1	4	10	22	19	
Ceftazidime-avibactam	8 ³	8 ³	10-4	13	13	
Ceftibuten (UTI only)	1	1	30	23	23	
Ceftobiprole	0.25	0.25	5	23	23	
Ceftolozane-tazobactam	1 ⁴	1 ⁴	30-10	23	23	
Ceftriaxone	1	2	30	25	22	
Cefuroxime iv ⁵ , <i>E. coli</i> , <i>Klebsiella</i> spp. and <i>P. mirabilis</i>	8	8	30	19	19	
Cefuroxime oral (uncomplicated UTI only)	8	8	30	19	19	

Mostly these antimicrobials are not very active systemically
 When they are concentrated in the urinary tract they can be active
 Always excluding urosepsis, but sometimes including pyelonephritis

Indication-specific breakpoints – agents also available for systemic use

Penicillins ¹	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)	
	S ≤	R >		S ≥	R <
Benzylpenicillin	-	-		-	-
Ampicillin	8 ¹	8	10	14 ^{A,B}	14 ^B
Ampicillin-sulbactam	8 ^{1,2}	8 ²	10-10	14 ^{A,B}	14 ^B
Amoxicillin	8 ¹	8	-	Note ^C	Note ^C
Amoxicillin-clavulanic acid	8 ^{1,3}	8 ³	20-10	19 ^{A,B}	19 ^B
Amoxicillin-clavulanic acid (uncomplicated UTI only)	32 ^{1,3}	32 ³	20-10	16 ^{A,B}	16 ^B

The only example of a systemic agent also having a UTI breakpoint
 One could argue that the SIR-definition implies that for e.g. carbapenems it is possible to treat uncomplicated UTI with standard dose if you end up in the I-category

However: surely 8 mg/L is not the limit of what you could achieve with a potent systemic agent if you give the drug in uncomplicated UTI????
 And what happens if you decide to double the dose in UTI?

What can be achieved in the urinary tract?

Urinary concentrations are very high



- RCTs with uncomplicated UTI show poor correlation with clinical breakpoints (Hooton TM, et al. JAMA 293:949– 955).
- Important to single out pyelonephritis where the outcome is worse if the strain is resistant by clinical breakpoints (Lee SS, et al. J Infect 2011; 62:159 –164 and Yang YS, et al. J Microbiol Immunol Infect 43:194 – 199)
- We try and avoid these drugs for uncomplicated UTI, but occasionally....

TABLE 1 Urinary concentrations of selected fluoroquinolones after oral administration^a

Antibiotic and dose (mg)	Urinary C_{max}^b (mg/liter)	Urinary trough concn (mg/liter)
Ciprofloxacin		
500	268 (130–967)	13 (5.1–37)
1,000 ^c	892.52 ± 476.4	32.80 ± 22.01
Levofloxacin		
500	498.89 ± 246.93	112.49 ± 52.5
500	406 (202–1,002)	84 (41–299)

^a Data are from references 19 and 20 and are mean values ± standard deviations or medians and ranges.

^b C_{max} , maximum concentration.

^c Ciprofloxacin XR.

Wenzler E, Danziger LH. AAC 2016; 60:2596 –2597

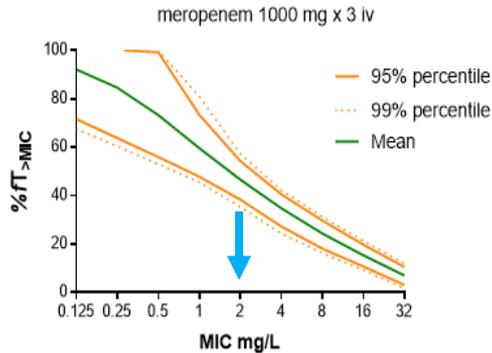
Table III. Urinary concentrations of meropenem (mg/L) following the first and tenth im dose (500 mg) in ten patients (mean ± s.d.)

Dose	Time period (h)			
	0–2	2–4	4–6	6–8
1st	328.4 ± 114.7	553.1 ± 243.2	198.6 ± 115.8	57.5 ± 44.5
10th	355.6 ± 175.3	726.7 ± 300.4	276.2 ± 175.5	97.4 ± 74.3

Novelli A et al. JAC 1996;37:775

What can be achieved systemically?

Systemic therapy – the example of meropenem

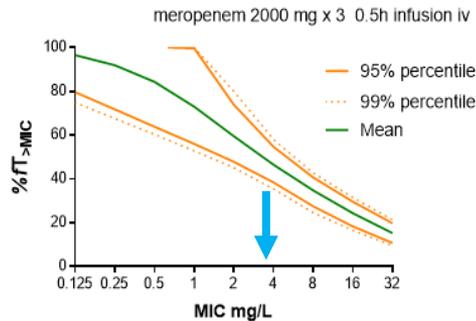


The following pharmacokinetic parameters were used to obtain the PTA (Wijma, 2018, based on data from Krueger, 2005)

Vc : 10.5 L, CV 17.7%
Cl : 15.6 L/h, CV 15.3%
Q : 7.17 L/h, CV 66.8%
Vp : 5.09 L, CV 44.9%

Fraction unbound (Fu): 90%
Infusiontime 0.5 h
Note : Covariance matrix used in simulations

$S \leq 2$ mg/L



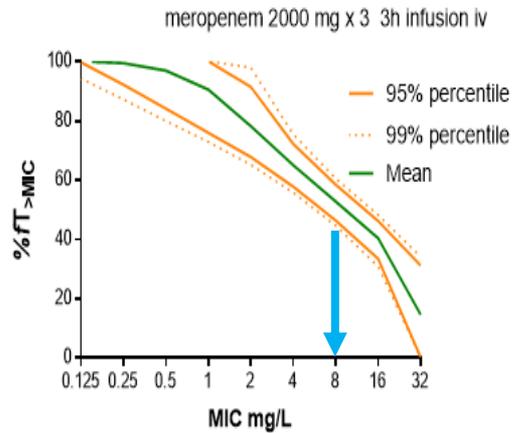
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$I = 4$ mg/L

But what about extended infusion?



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Cl: 15.6 L/h, CV 15.3%

Q: 7.17 L/h, CV 66.8%

Vp: 5.09 L, CV 44.9%

I=8 mg/L
(R>8 mg/L)

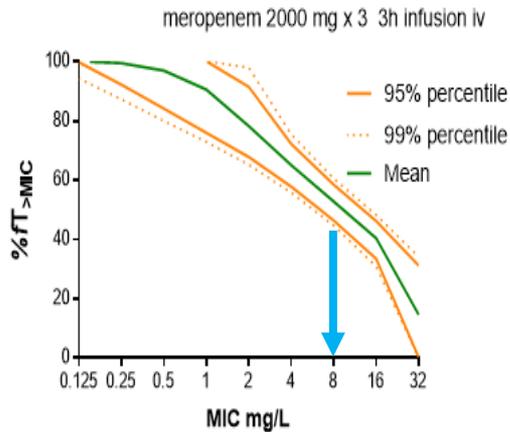
Fraction unbound (Fu): 90%

Infusion time 0.5 h

Note : Covariance matrix used in simulations

EUCAST 2018 (consultation document; J. Mouton)

And what about if the MIC is >4 mg/L?



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Vc: 10.5 L, CV 17.7%
 Cl: 15.6 L/h, CV 15.3%
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 Vp: 5.09 L, CV 44.9%

I=8 mg/L
 (R>8 mg/L)

Fraction unbound (Fu): 90%
 Infusion time 0.5 h

Note : Covariance matrix used in simulations

EUCAST 2018 (consultation document; J. Mouton)

And what about if the MIC is >8 mg/L or the target is higher than $fT > MIC$ 40%

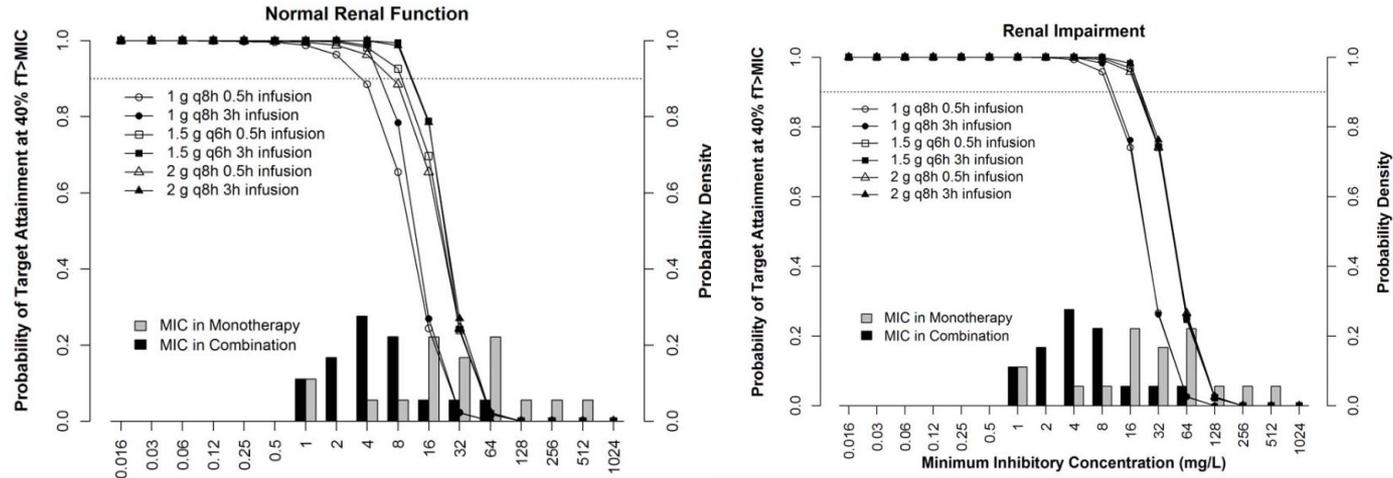
- Patient with septic chock caused by *P. aeruginosa* (emanating from VAP)
- Incremental increase in meropenem MIC up to 8 mg/L
- Higher target than applied for general breakpoints (4xMIC instead of MIC)
- Combination of 3 g, extended infusion, and q6h (instead of 8h) dosing
- Taccone FS. AAC 2012; 4: 2129

TABLE 1 Meropenem regimens, concentrations, and pharmacodynamics during therapy^a

Day of therapy	MEM dose	Time of sampling	MEM concn (mg/liter)	MIC (mg/liter)	% T > 4× MIC
1	1 g q8h				
2	1 g q8h	2 h 8 h	12.3 <2.0	2	37
5	1 g q8h	2 h 8 h	13.4 <2.0	2	39
9	2 g EI q8h	3 h 8 h	17 3	4	39
15	3 g EI q6h	3 h 6 h	43 19	8	51

^a MEM, meropenem; q8h and q6h, every 8 h and 6 h; EI, extended infusion (over 3-h period); 2 h, 3 h, 6 h, and 8 h, 2, 3, 6, and 8 h after the onset of MEM administration; T > 4× MIC, time above 4 times the MIC.

Challenging strains with carbapenemases – KPC-2



Albeiro J et al. AAC. 2016;60(7):4128-39.

Novel antimicrobials and selection of dosing regimens

Two novel antimicrobials vs carbapenemase-producing Enterobacterales

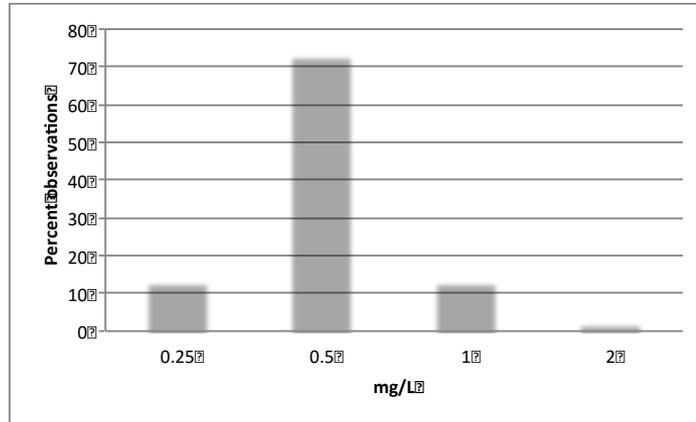
Antimicrobial (regimen)	Breakpoint	Mother compound	Breakpoint
Ceftazidime-avibactam (2 g 8h, prolonged infusion)	S \leq 8 mg/L, R>8 mg/L	Ceftazidime (1 or 2g q8h, standard infusion)	S \leq 1 mg/L, R>4 mg/L
Meropenem-vaborbactam (2 g q8h, prolonged infusion)	Not defined yet	Meropenem (1 or 2g q8h, extended infusion)	S \leq 2 mg/L R>8 mg/L

Why not breakpoints of 1/8 for ceftazidime?
Would make many ESBLs treatable....

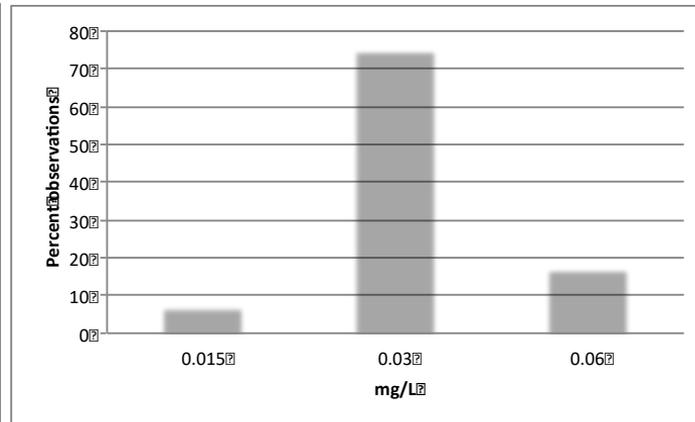
Can we trust the MICs in the resistant population?

Reproducibility of broth microdilution

K. pneumoniae

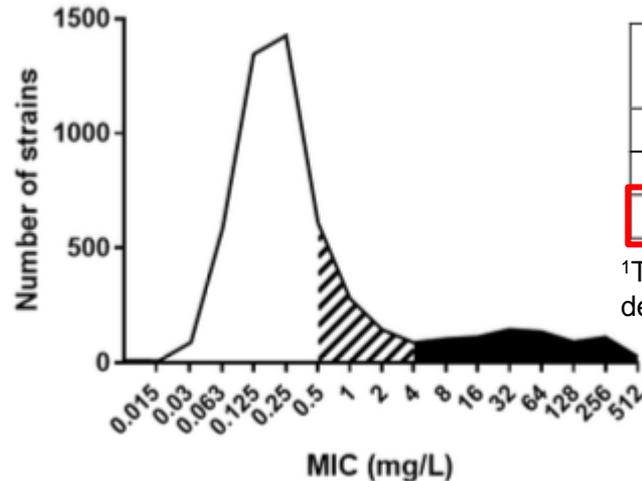


E. coli



JMI Laboratories (courtesy of Prof R. Jones)

Not only variation in serum concentration should be taken into account...



MIC found	Interpretation for target attainment
Within WT. < ECOFF	ECOFF
>ECOFF	MIC + two 2-fold dilutions ¹

¹The number of dilutions could be higher or lower than two depending on proficiency of the lab and the drug-species distribution

- Variability: both technical and biological
- Usually not taken into account in recommendations regarding individualized dosing based on high-quality TDM

What does the future hold for breakpoint tables?



Future breakpoint tables

Antimicrobial	S	I	R
Meropenem	≤ 2 mg/L (1 g q8h)	4-8 mg/L (2 g q8h, prolonged infusion)	> 8 mg/L
Meropenem uncomplicated UTI	≤ 32 mg/L (1 g q8h)	64 mg/L (2 g q8h, prolonged infusion)	> 64 mg/L
Meropenem supranormal	≤ 16 mg/L (3 g q8h, prolonged infusion)	32 mg/L (3 g q6h, prolonged infusion)	> 32 mg/L

Caveats: critically ill patients with altered PK and need of a higher PD-target
 Challenge: lab information systems, communication to clinicians

Conclusions

- For uncomplicated UTI the breakpoints for agents that are also used systemically are far too conservative
- With many non-toxic agents (most notably beta-lactams) the potential is high to increase exposure through supranormal dosing
- Several additional dilution steps of MICs can be covered with supranormal dosing regimens
- Beware that MICs may be variable, particularly outside the wild-type population (add one dilution step)
- Can we deal with breakpoint tables with even higher complexity
- Can we with the paucity of new agents afford not to try making more complex breakpoint tables?
- Should we have breakpoint tables for advanced users?