

**Can PK/PD provide all the answers for
breakpoints & antibiotic dosing?**

.... NO, IT CAN'T...!

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pK-pD principles are sound

Critical parameters

- β -Lactams, $fT > MIC$
- Aminoglycosides, $C_{max} : MIC$
- Most others, $AUC : MIC$

BUT

- Magnitude of required parameter uncertain
- Some parameters – MICs especially – very imprecise
- Human patients are more variable than mouse thighs
- Real practice error prone

β -Lactams- what do you need?

- 40% $fT > MIC$ widely quoted for normal patients....
Used to define breakpoint.
- Company with new β -lactam will assert lower value
- In severe infections longer $fT > MIC$ may be needed...
- Ceftazidime: 82% cure @ $fT > 100\%$, vs. 33% if less
- Cefepime: 97% cure @ $fT > 100\%$ vs. 44% if less
- Meropenem: Responders had $fT > MIC$ 83%, failures, 60%
- “I’m a two log man; he’s a one log man”*

McKinnon et al., IJAA 2008;**32**:345

Goncalves-Pereira, Povia *Crit Car Med* 2011;**15**:R206

Ariano et al., *Ann Pharmacother* 2005;**39**:32

*Drusano, recent advisory board

Some limits to MICs

- **MICs determined on doubling dilution scale**
 - MIC of 1 means 0.51 to 1.00; average is <1
 - Accept MICs as ± 1 doubling dilution
- **Determined by standard, but arbitrary, methods**
 - Why MH broth? MICs in IsoSensitest are lower
 - Why inocula of 10^4 - 10^5 for all infections?
 - Why broth, not agar? Discs are on agar
- **MICs in pK/pD studies determined centrally**
 - Real practice; zones determined locally; more variable

E. coli NCTC13352. K-12 derivative with TEM-10, a ceftazidimase

	MIC mg/L
Ceftazidime	>128
Cefotaxime	1-2
Ceftriaxone	1-2
Cefepime	2-4

4 labs each did disc tests 10 times...

NCTC13352: cefotaxime 30 μ g discs: 10 tests/lab

	Mean zone (mm)	SD (mm)	S ≥ 30	I 24-29	R ≤ 23
Lab 1	28.7	0.82	1	9	0
Lab 2	29.4	0.97	6	4	0
Lab 3	25.9	1.29	0	10	0
Lab 4	31.3	1.06	10	0	0

Data courtesy Jenny Andrews, Birmingham

NCTC13352: cefepime 30 μ g discs: 10 tests/lab

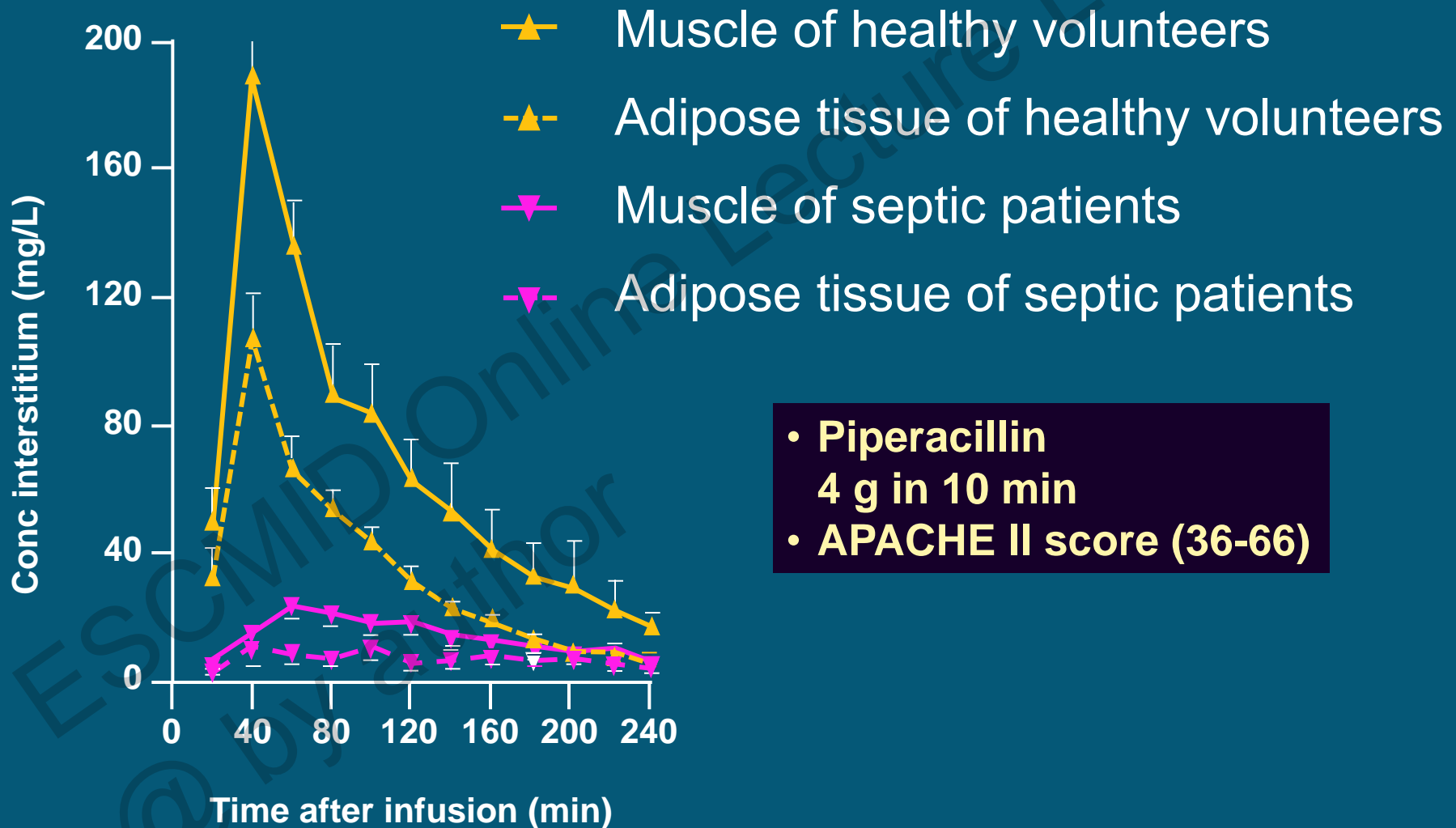
	Mean zone (mm)	SD (mm)	S ≥ 32	I 27-31	R ≤ 26
Lab 1	26.4	0.52	0	4	6
Lab 2	28.1	0.74	0	10	0
Lab 3	23.0	1.55	0	0	10
Lab 4	29.1	1.00	0	10	0

Data courtesy Jenny Andrews, Birmingham

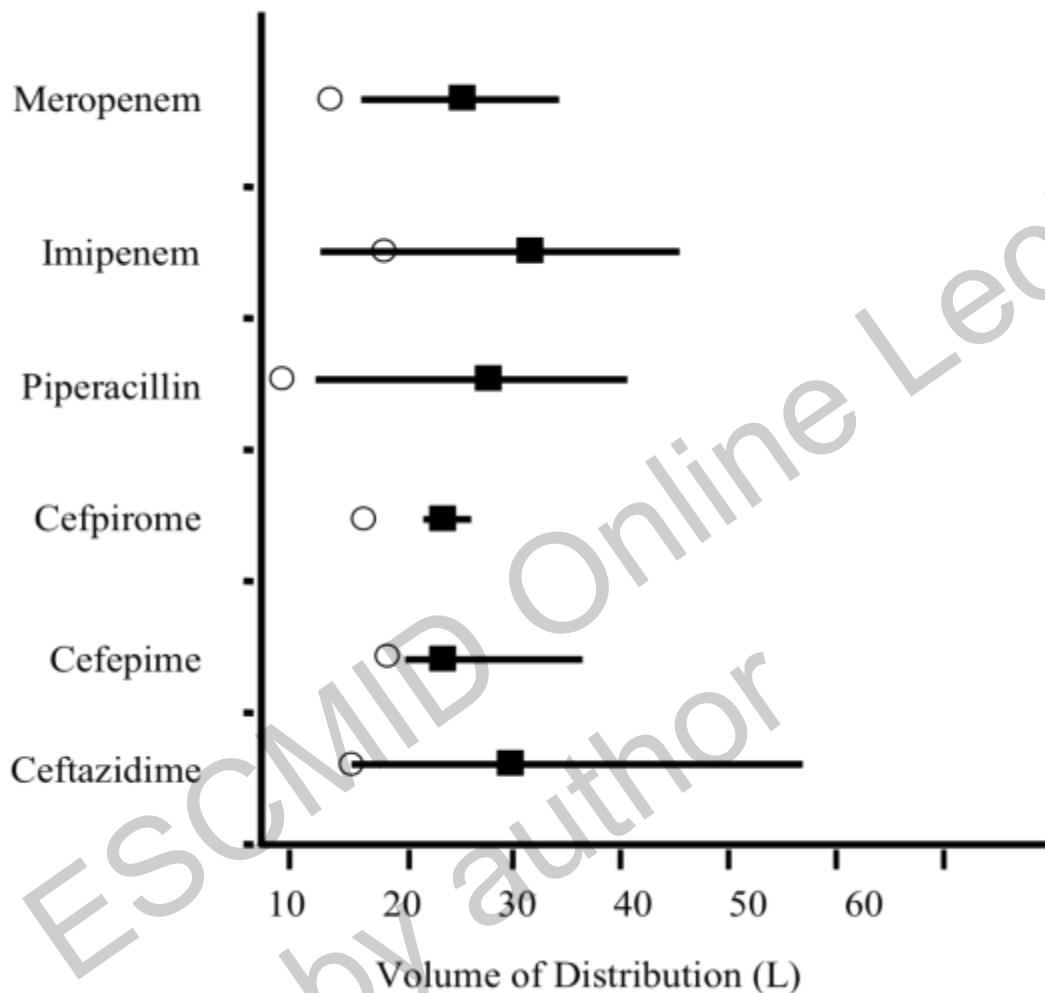
Carbapenem R_x in infections with KPC *Klebsiella*

Patient	Site	MIC imipenem		Days imipenem	Outcome
		Vitek	Etest		
M76	Respiratory	2	0.25	7-mero	Failed
M82	Blood	4	2	14	Cure
M92	Respiratory	4	2	3	Cure
F64	Respiratory	4	2	12	Failed
F69	Respiratory	4	8	6	Failed
F46	Blood	4	8	7	Cure
M77	Respiratory	4	≥32	7	Failed
F61	UTI	2	≥32	7	Cure
M52	UTI	4	16	14	Failed
F60	Blood	≥16	8	10-mero	Failed
M60	Respiratory	≥16	8	7-mero	Cure

Sepsis & antibiotic pK



Volume of distribution: β -lactams in ICU patients



- Weighted means of ICU studies
- Bars, range of means of individual studies
- Results for healthy volunteers

Using prisoners to find the right parameter for penicillin vs. GC

- Gonococcal urethritis in male prisoners
- Varied penicillin dosage
- Cure required 4 x MIC for 7-10h
- Penicillin 75-80% protein bound
- Equates to free drug @ 1 x MIC for 7-10h
- Suggests penicillin effective up to MIC = 1 mg/L

Monte-Carlo simulations for cefixime vs. gonorrhoea

MIC mg/L	<i>f</i> T > MIC for cefixime 400 mg p.o.		
	Median	95% CI	
0.015	28.5	23.9	35.0
0.03	25.2	21.1	30.8
0.06	21.8	18.2	26.8
0.125	18.4	15.3	22.7
0.25	14.9	12.3	18.3
0.5	11.4	9.0	14.2
1	7.5	5.0	9.8
2	1.1	0	5.1

But is 7-10h cover adequate for cephalosporins?

- Japan
- Male urethritis
- Cefixime 2 x 200 mg q6h

MIC (mg/L)	Cures
≤ 0.06	45/45
0.12	6/11
≥ 0.25	2/3

Why does cefixime start to fall over 2 dilutions before it should?

“Maybe patients slip second tablet in partner’s tea?”

So, look at 400 mg p.o. stet cefixime in Canada

- 25% failure (7/28) at MIC \geq 0.12 mg/L
- 1.9% failure (2/105) at MIC < 0.12 mg/L
- Maybe 7-10h cover isn’t right for cefixime?
- Maybe pK parameters aren’t right?

Either way, gonorrhoea is the simplest bacterial infection

Missed antibiotic doses

- 45 Acute Care Trusts
- 5899 patients, 21390 antibiotic doses prescribed
- 5.2% doses omitted
- 13.2% of patients had ≥ 1 missed dose

Fundamental pK/pD tenets are valid

BUT

- We overestimate precision.... MICs, $fT > MIC$
- We underestimate patient variability and errors
- Might be OK we monitored every patient's levels
 - Too expensive
- ?? Better to view susceptibility results as relative
- Favour the most active agent; allow margin