Impact of resistance on treatment and dosing decisions

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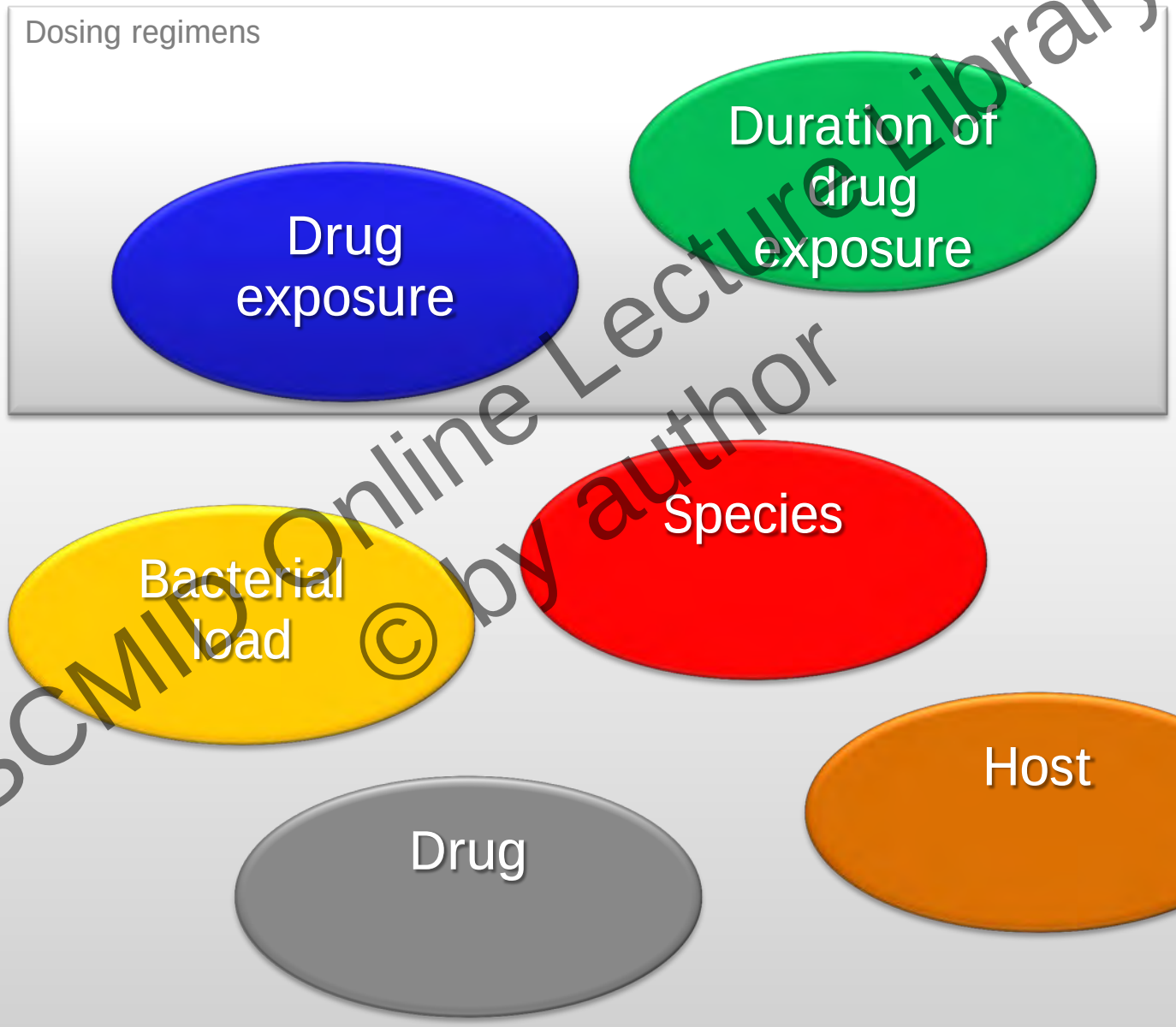
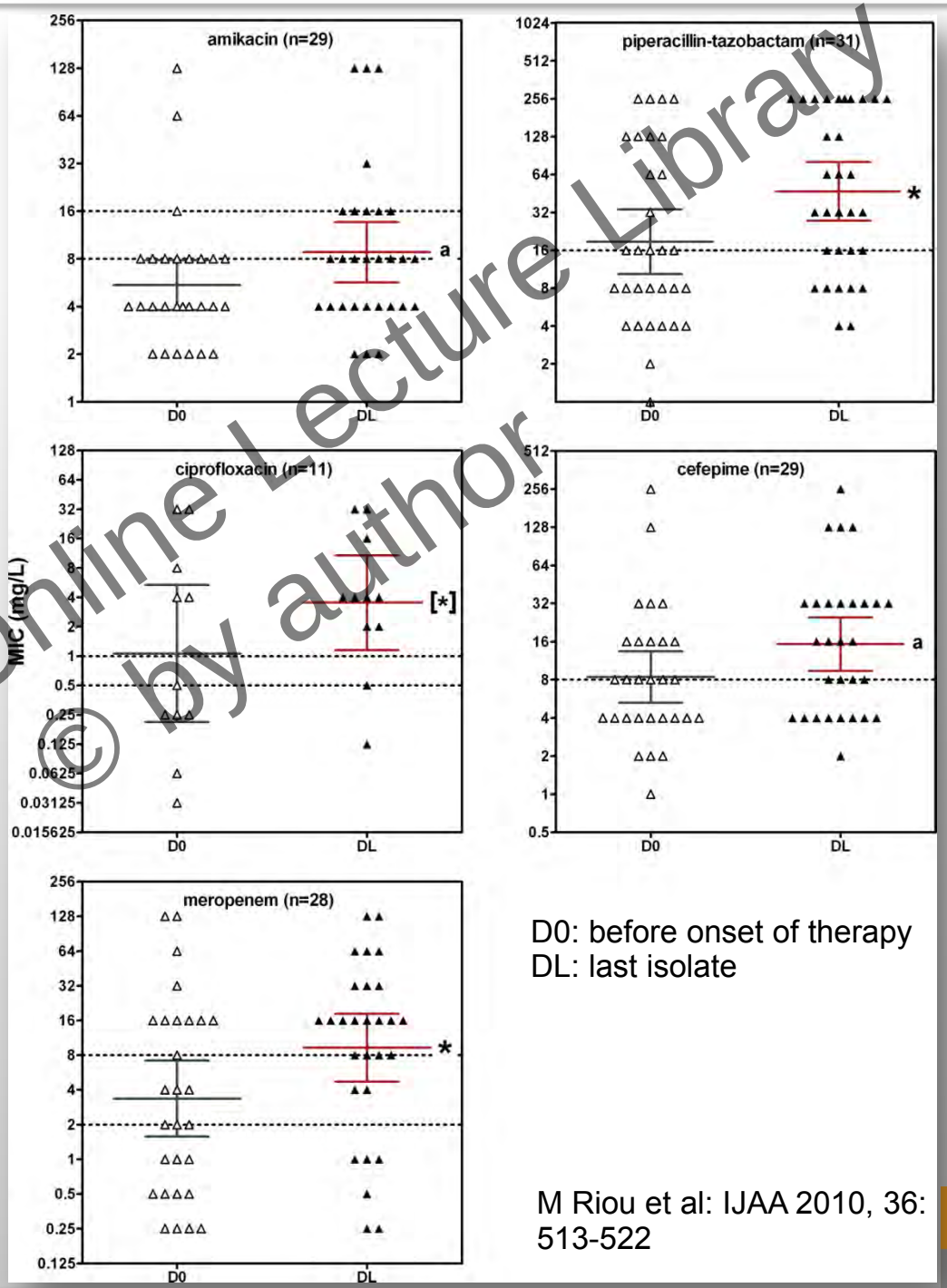
Emergence of resistance



Emergence of resistance

Pseudomonas HAP/VAP inf
Standard dosages in ICU



D0: before onset of therapy
DL: last isolate

M Riou et al: IJAA 2010, 36: 513-522

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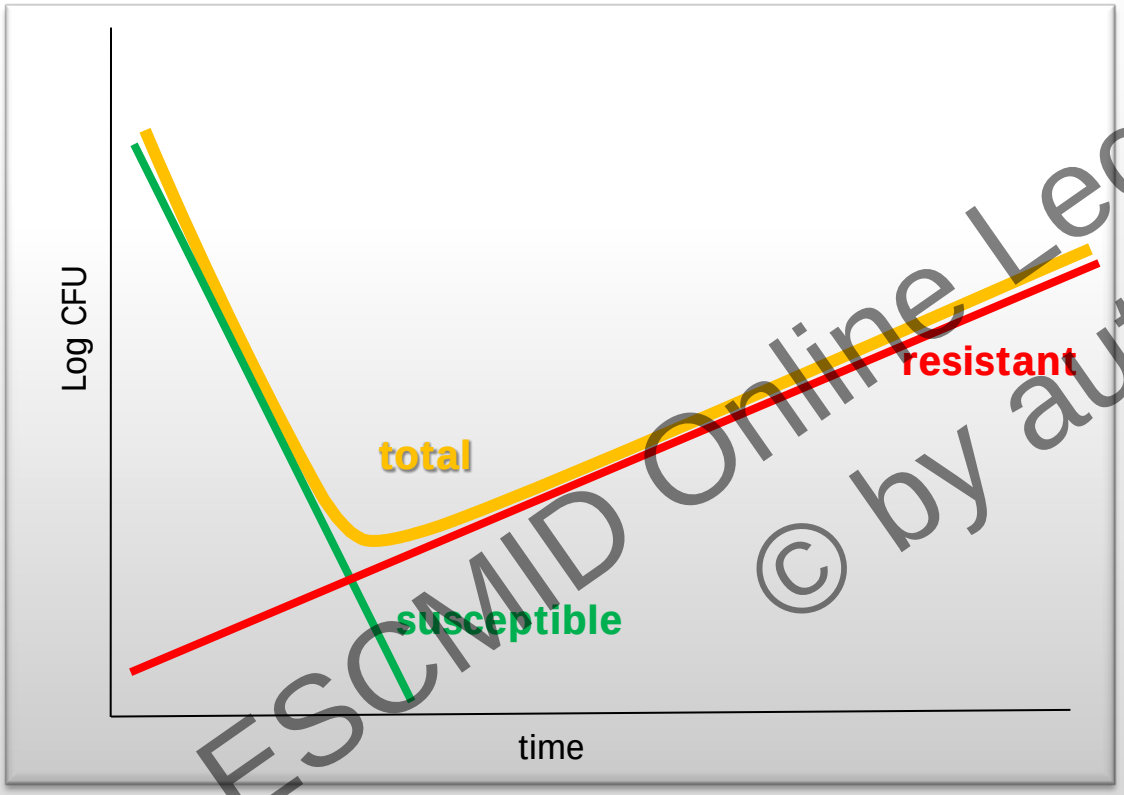
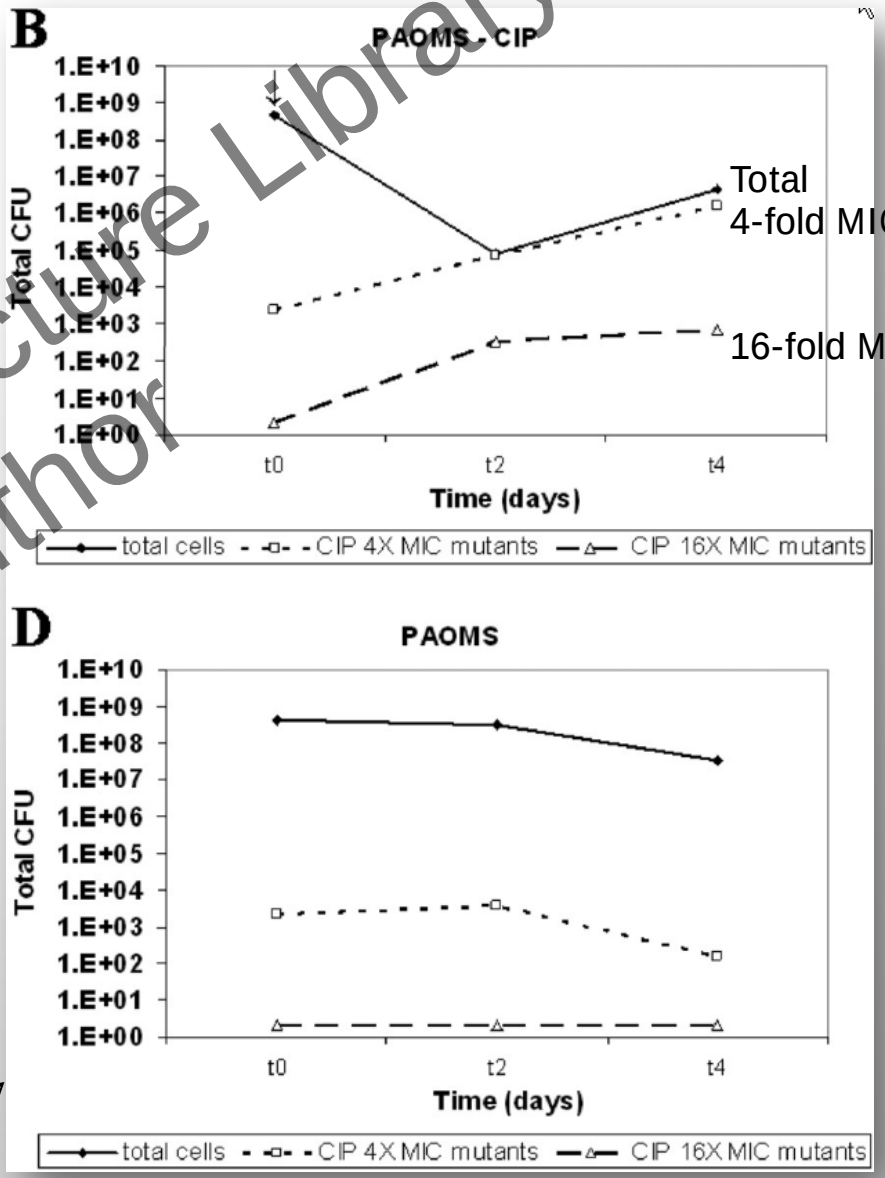
Bacterial population analysis



G. Drusano: Nat Rev Microbiol 2004; 2:289–300

2 µg Ciprofloxacin - Pseudomonas



Control

Macià M D et al. AAC 2011;55:5230-5237

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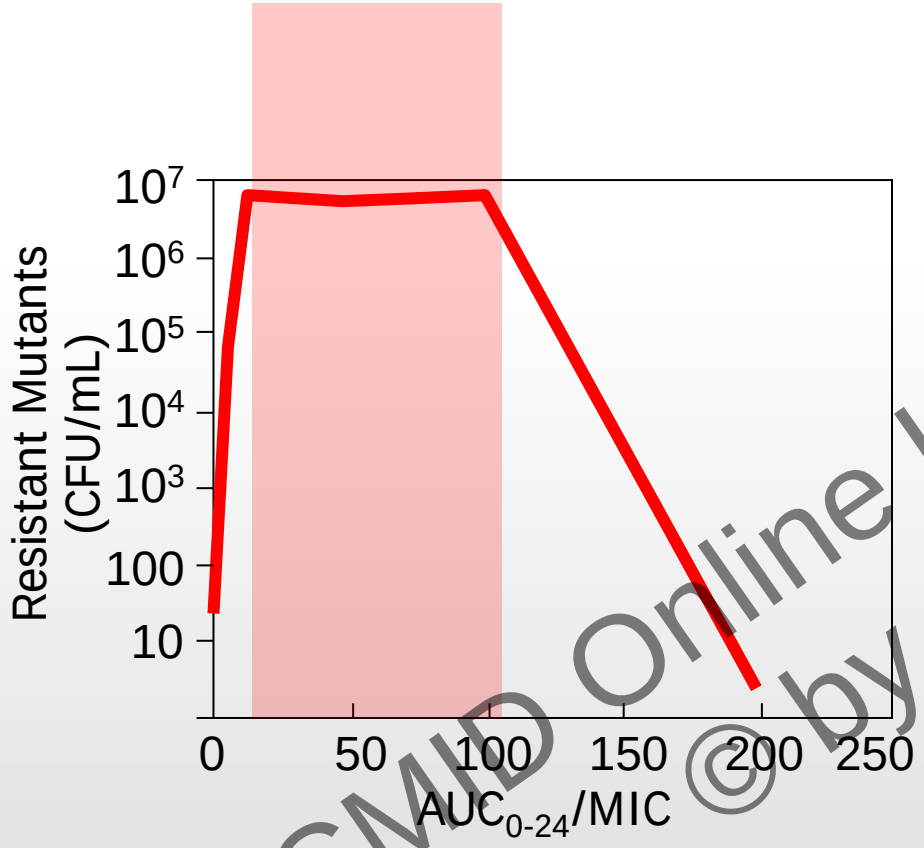
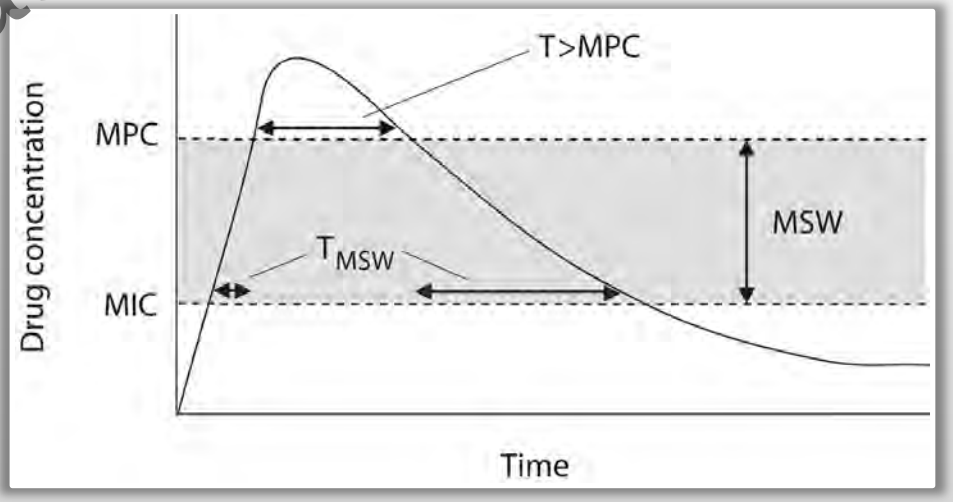
Drug exposure - Selection of resistance



V. Tam, G. Drusano et al

Selection of resistant mutants when drug concentrations are within the MSW



SK Olofsson, O Cars: CID 2007;45:S129-S136

Example - Clinical Case

Renal transplant patient with recurrent urosepsis over a period of 4 months

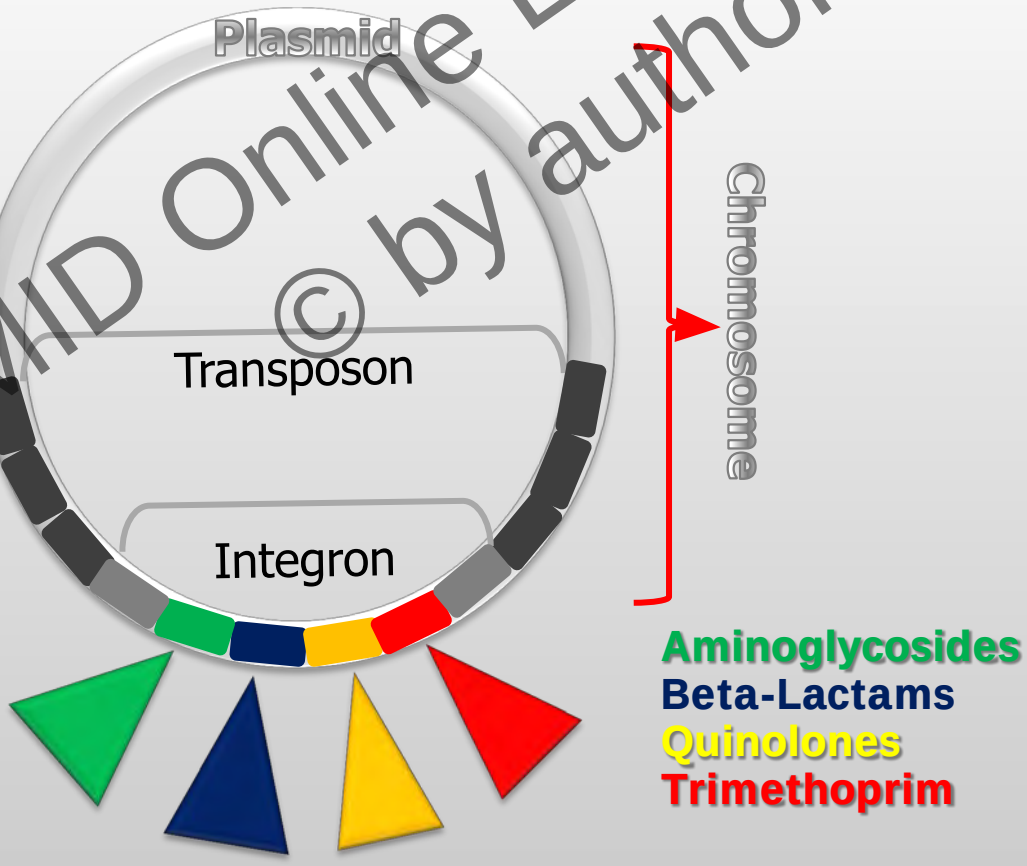
Day 1	Surgical prophylaxis: cefazolin 1g			
	Postoperative fever: **levofloxacin 250 mg q12 h**			
Day 7		K1 U	ESBL-producing K. pneum.: res. cipro, genta	SHV-12, TEM-1
	imipenem-containing regimen (**250 mg q6 h**) for 2 weeks			
Day 11		K2 U	Imipenem MIC↑	MBL (VIM-1)
Day 14		K3 U	As K2	
Day 25		K4 U	Resistant to all ß-lactams (fully resistant to imi)	
	tigecycline (100 mg/ 50 mg q12 h for 1 week)			
Day 32		K5 B	Res tigecycline	
Day 36		K6 B	As K5	
	ertapenem 1 g q24 h			
Day 74		K7 B K8 B	As K2 (Imipenem MIC↑) Suscept. imipenem, res tigecycline	
Day 81		K9 B	As K7	

C. Rodríguez-Avial et al: CMI 2012;18(1):61-6

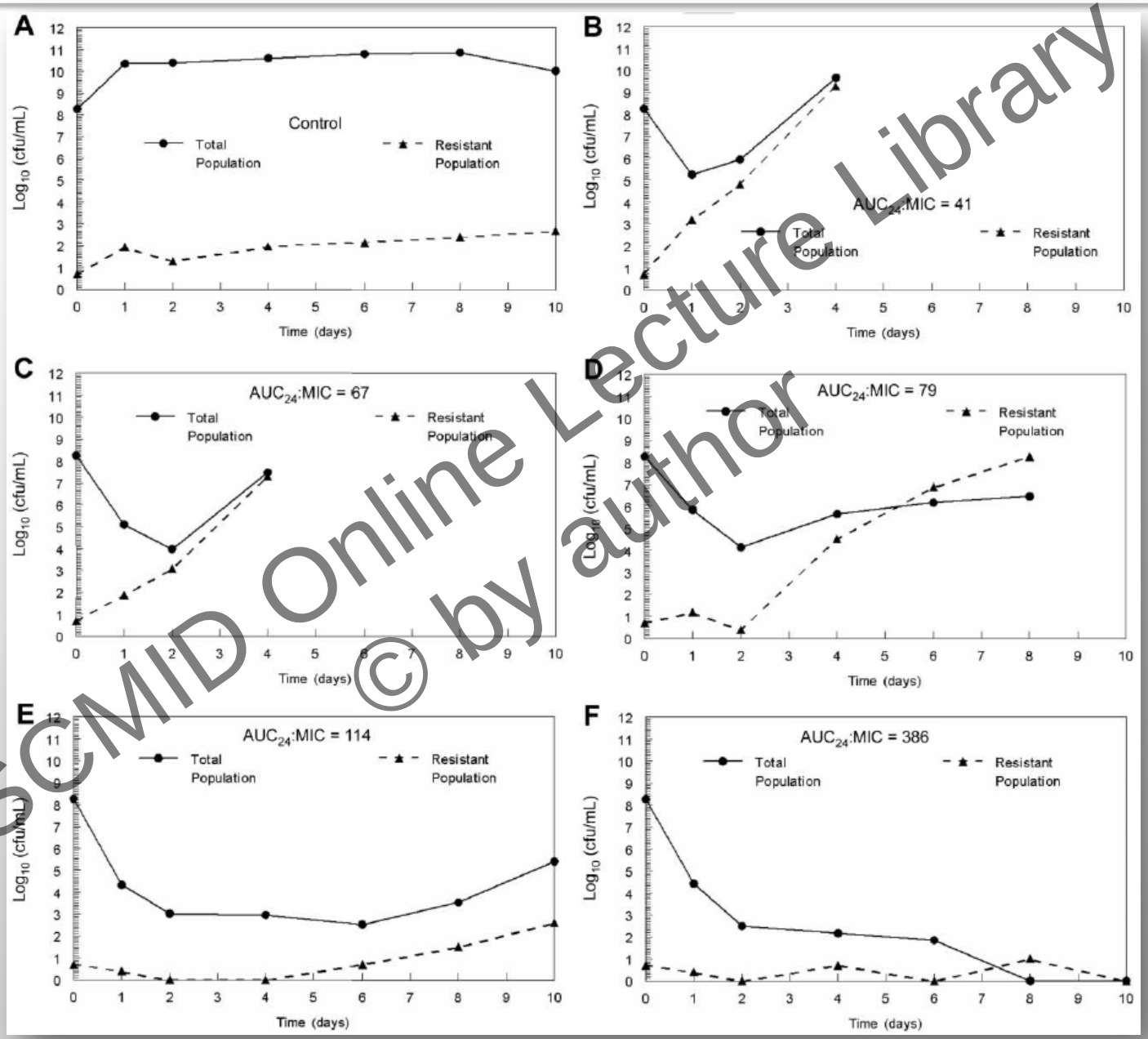
Cross-resistance, Co-resistance

ESBL-producing Klebsiella

- Extended-spectrum ß-lactamases: all penicillins, all cephalosporines (more or less), monobactams
- > 70% co-resistant to unrelated classes



Exposure – resistance relationship



Garenoxacin
S. aureus

Duration of therapy !

V Tam et al: JID 2007;195:1818–27

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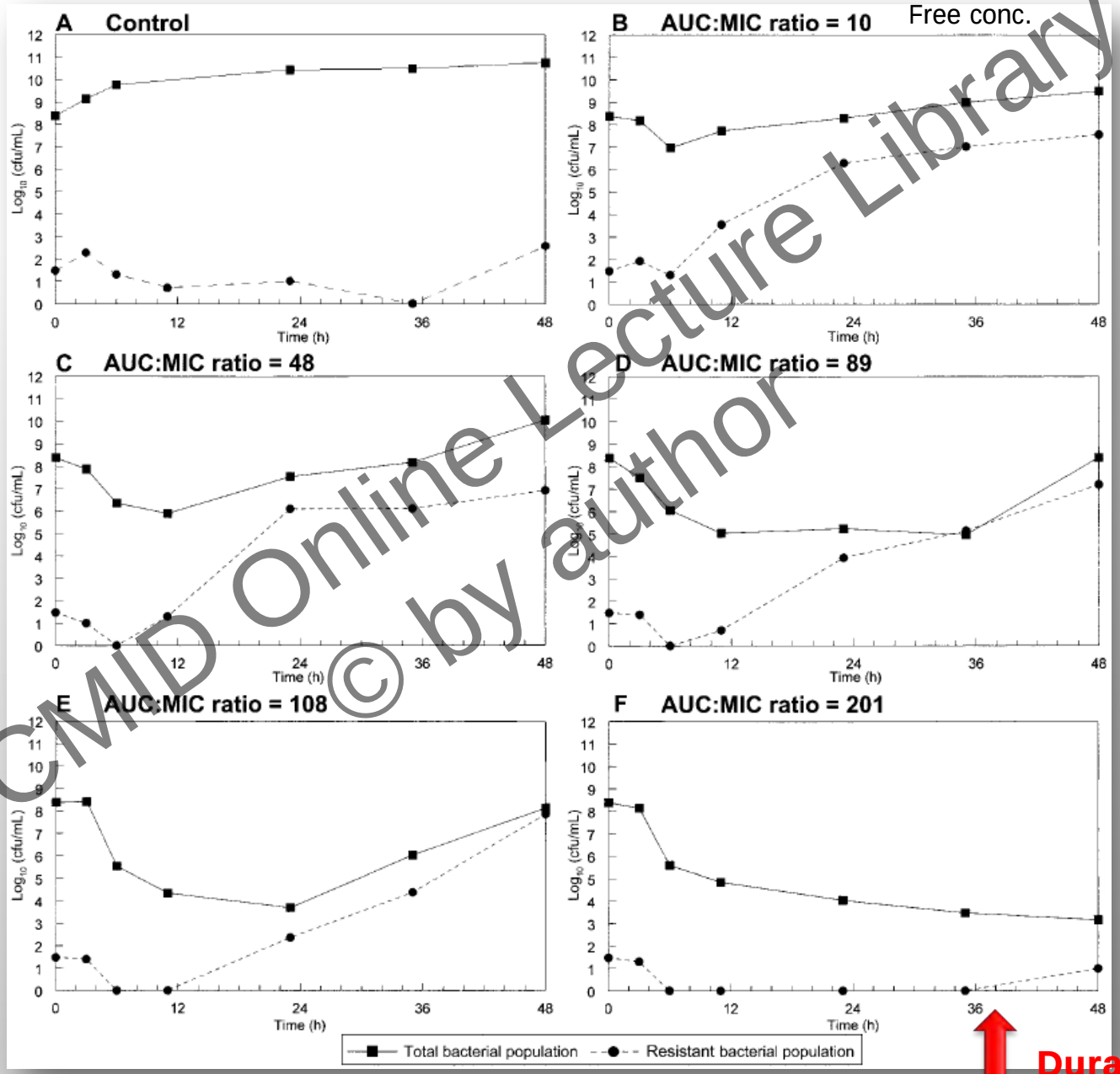
Exposure – resistance relationship



Garenoxacin
P. aeruginosa

Duration of therapy !

V Tam et al: JID 2005;192:420–8

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PK - Quinolones

Levofloxacin 750mg qd healthy volunteers	*f*AUC ~ 125 mg.h/L
Levofloxacin 500 mg qd 12 patients with VAP	*f*AUC 50±15 mg.h/L
Ciprofloxacin 800mg daily patients	AUC 45 (23–128) mg.h/L
Ciprofloxacin 400mg td patients	AUC ~110±40 mg.h/L
Ciprofloxacin 400mg bd patients	AUC ~70±30 mg.h/L
Moxifloxacin 400mg qd volunteers	AUC ~40 mg.h/L

Benko R et al: IJAA 2007; 30:162-168
Haeseker MB et al: Br J Clin Pharmacol 2012;75:180–185
Saengsuwan P et al: J Med Assoc Thai. 2010 ;93:784-8
Stass H et al: Br J Clin Pharmacol. 2002;53:232–237

Clinical case – Dosing

Renal transplant patient with recurrent urosepsis over a period of 4 months

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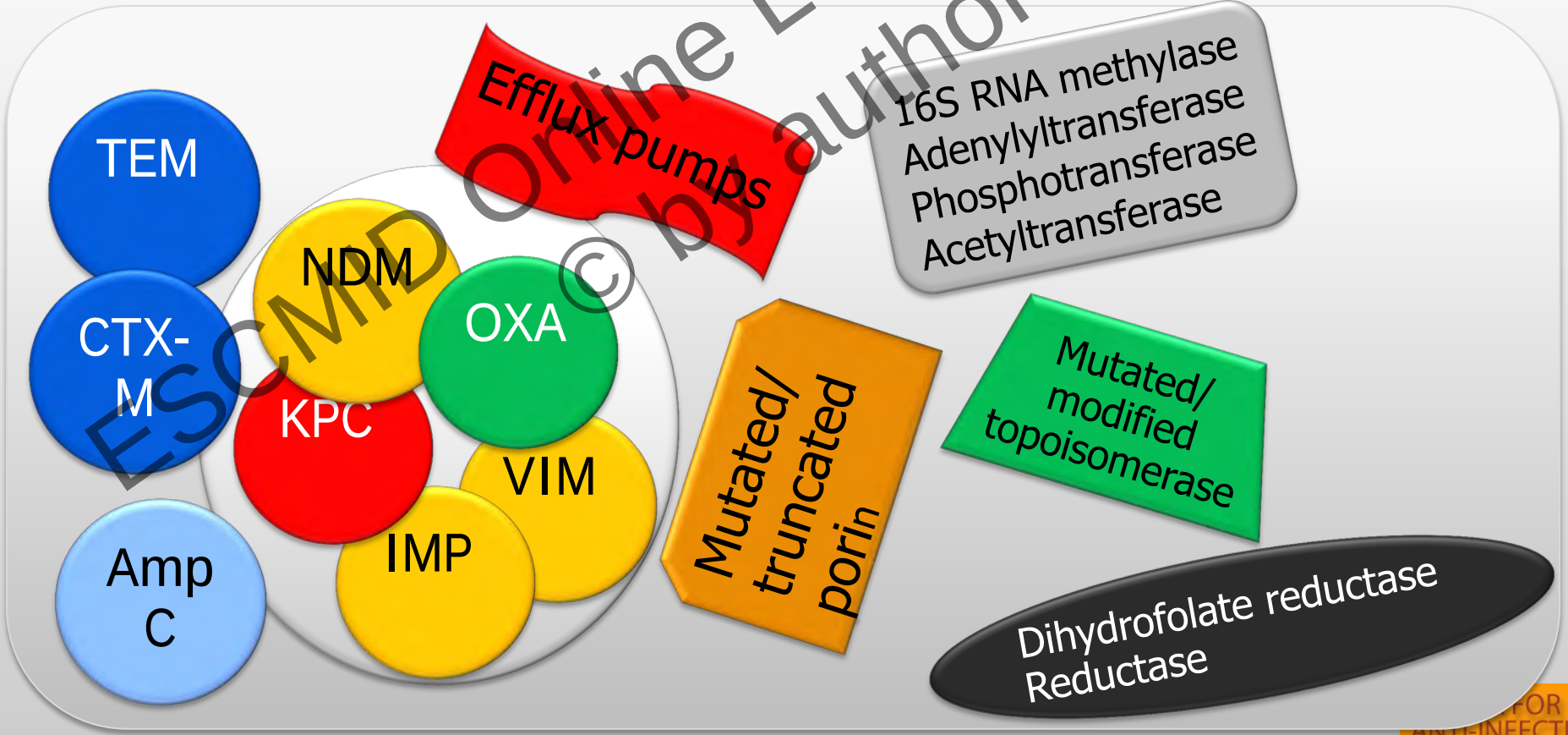
C. Rodríguez-Avial et al: CMI 2012;18(1):61-6

Cross-resistance, Co-resistance

ESBL-producing → MBL producing Klebsiella

CRE

- Extended-spectrum ß-lactamases: all penicillins, all cephalosporines (more or less), monobactams
- Carbapenemase: Additional resistance to all ß-lactams including carbapenems

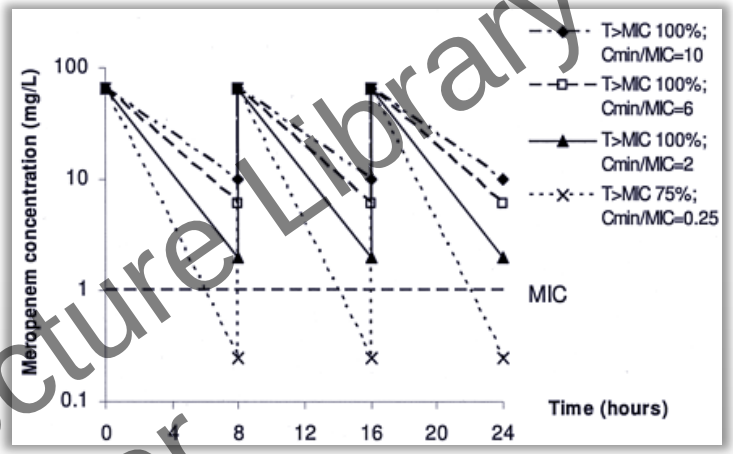


L. Poirel et al AAC 2011; 55:4224-9

PK/PD - Selection of resistance

Meropenem - Pseudomonas

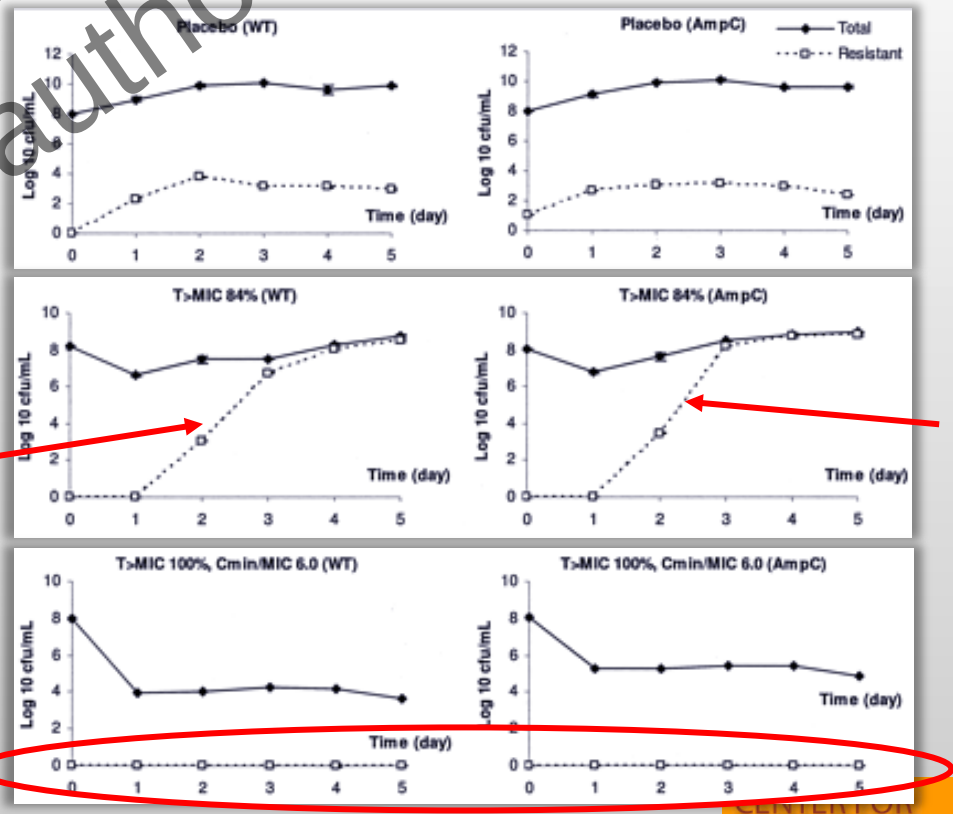
- P. aeruginosa: wild type + AmpC stably derepressed mutant (MIC = 1 mg/l)
- High inoculum, neutropenic



No selective pressure with placebo

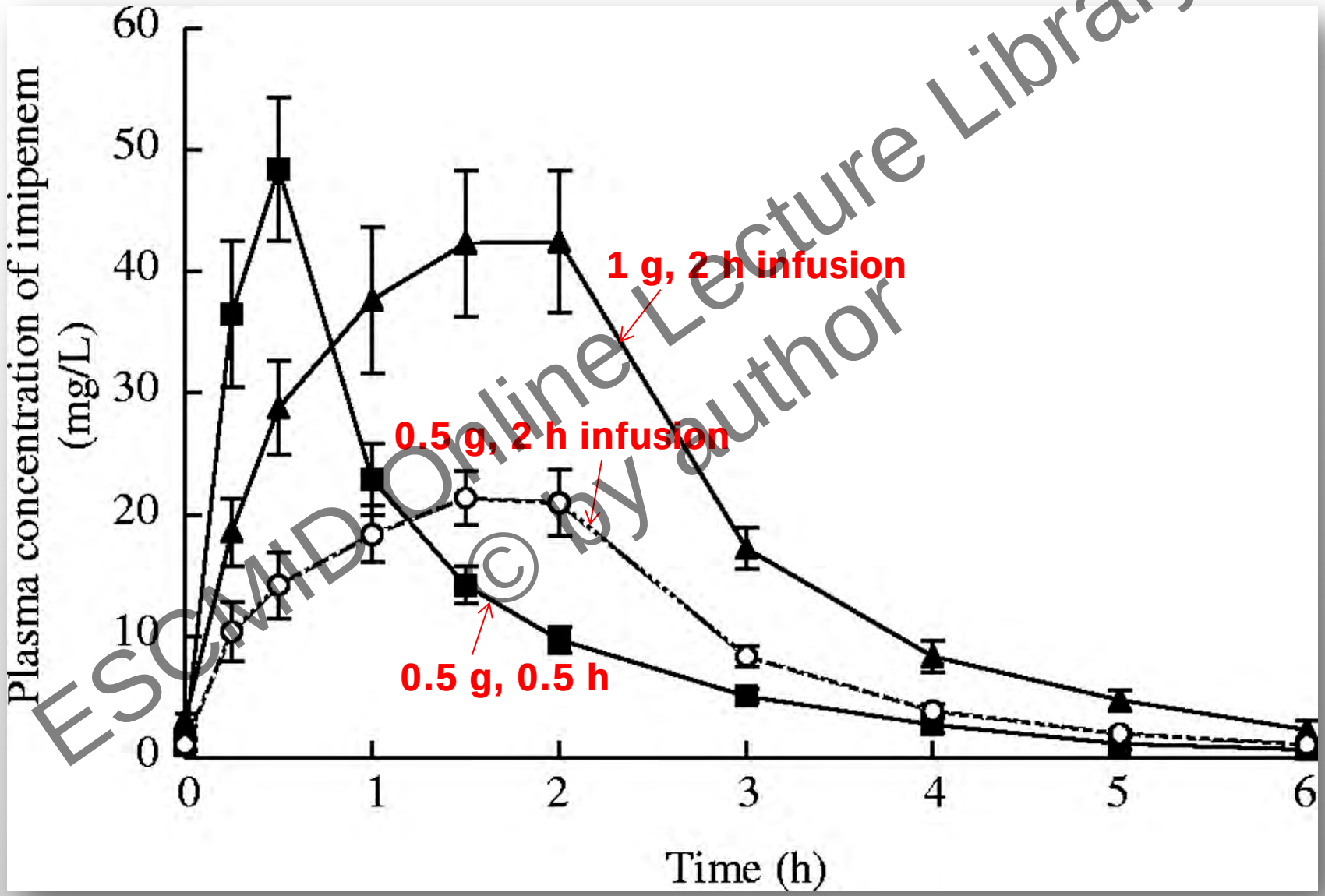
Suboptimal meropenem exposure T>MIC=84%: emergence of resistance

Optimized meropenem exposure **T>MIC=100%, C_{min}/MIC=6**: no growth



VH Tam et al: AAC 2005 (49), 12: 4920

Imipenem serum concentrations in volunteers



Jaruratanasirikul S et al. JAC 2005;56:1163-1165

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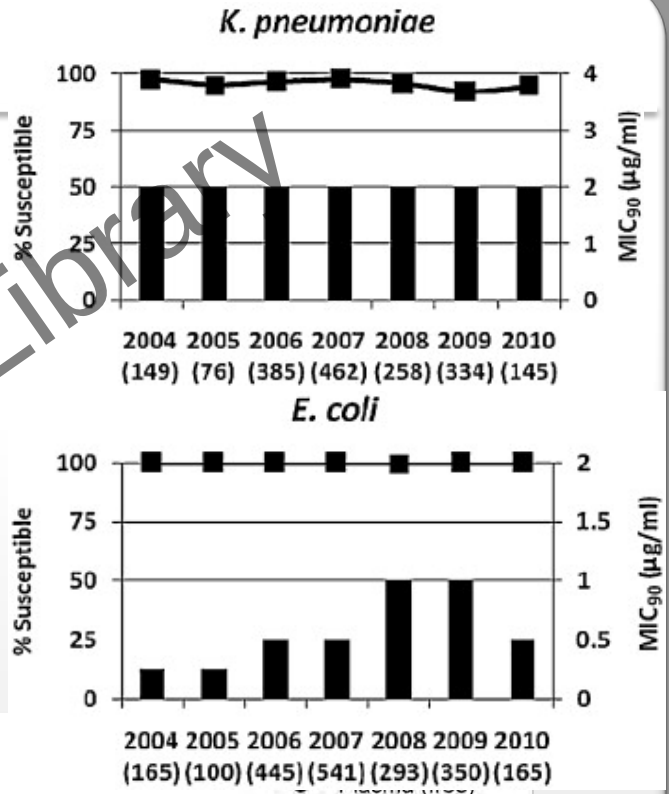
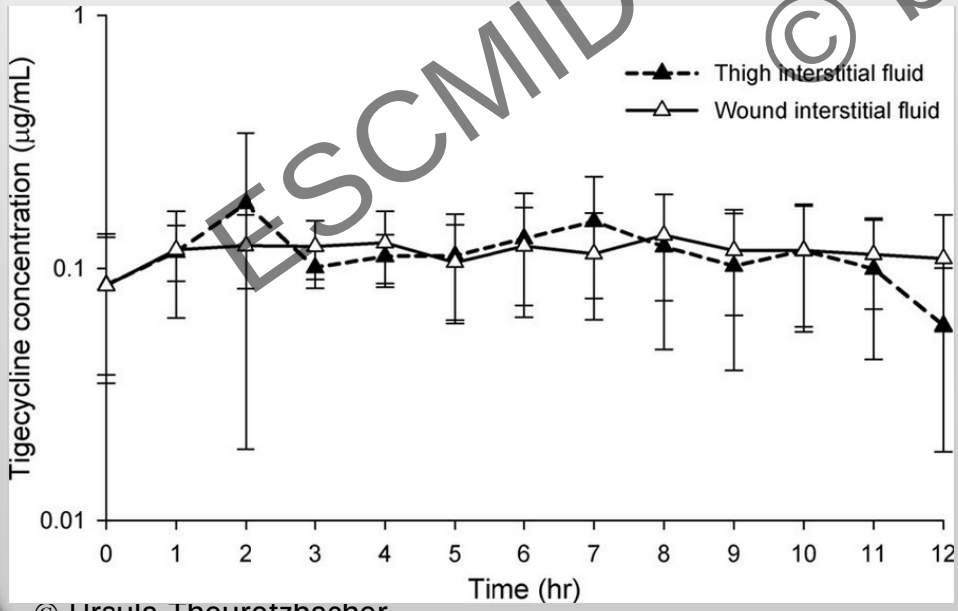
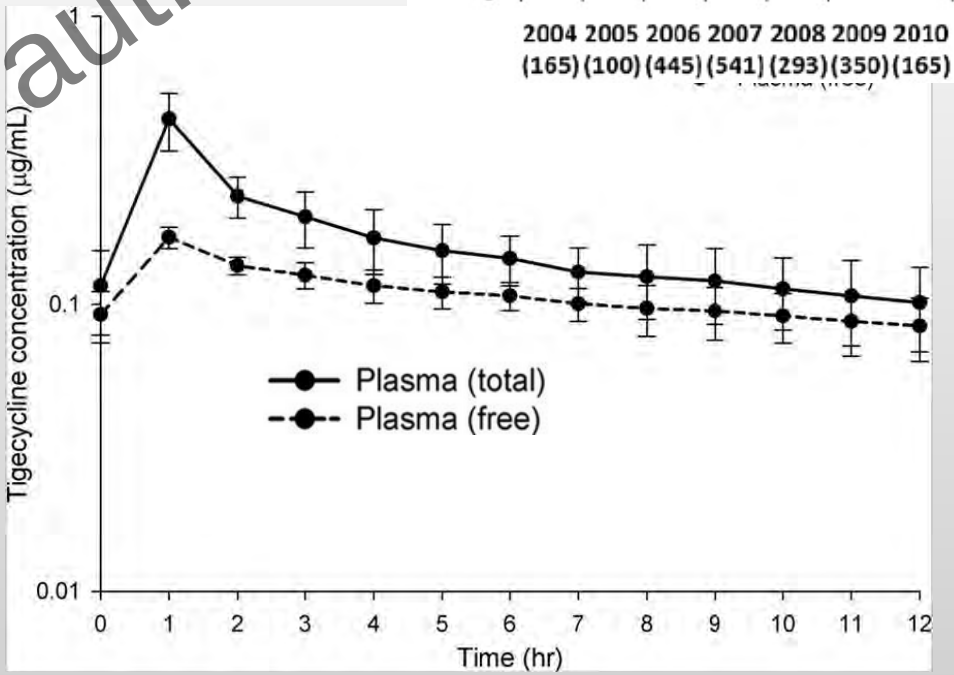
C. Rodríguez-Avial et al: CMI 2012;18(1):61-6

PK/PD - Tigecycline

- Resistance: up-regulated efflux
- In vivo resistance development reported
- Concentrations at site of infection, subinhibit. conc. (UTI, sepis, abdom.abscess)
  - Blood: C_{max}^{ss} 0.4-0.8 mg/L (total conc.)
  - Urin: 30%
  - Peritoneal fluid: ~50%



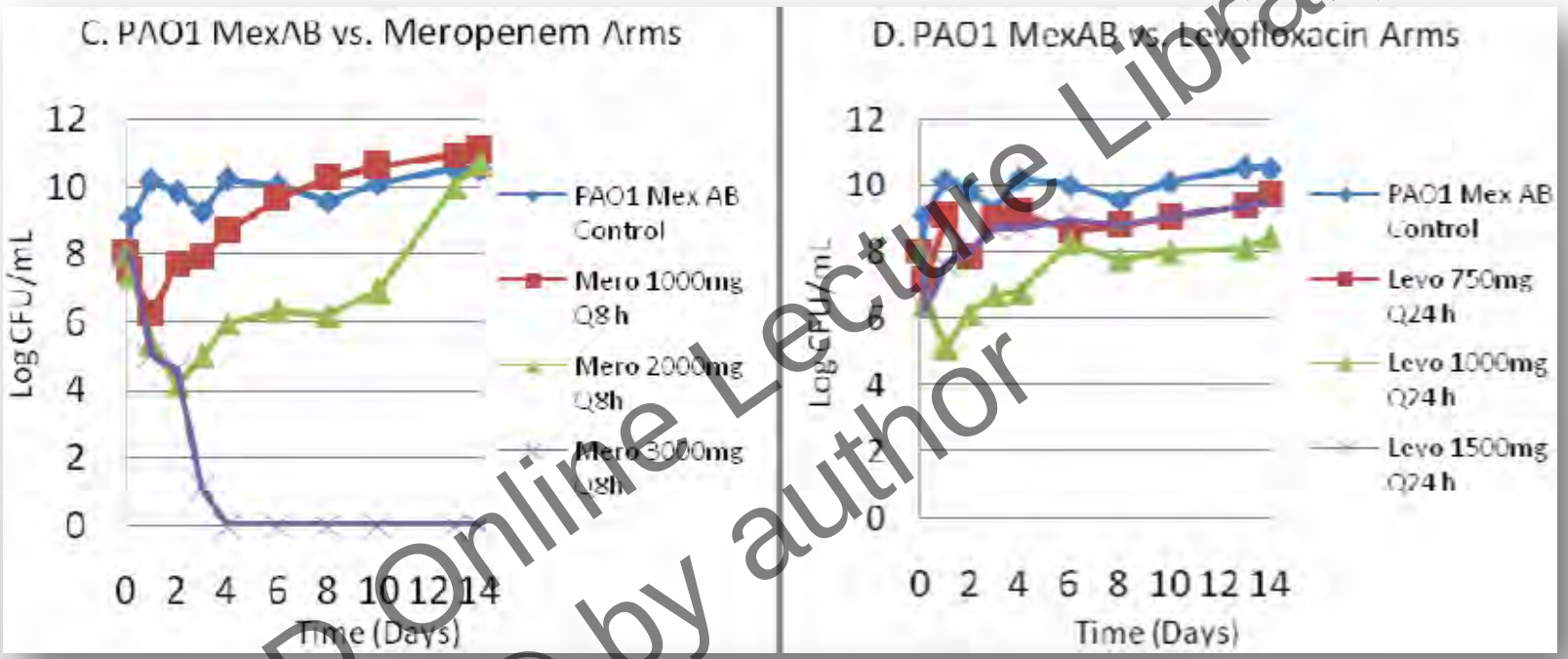


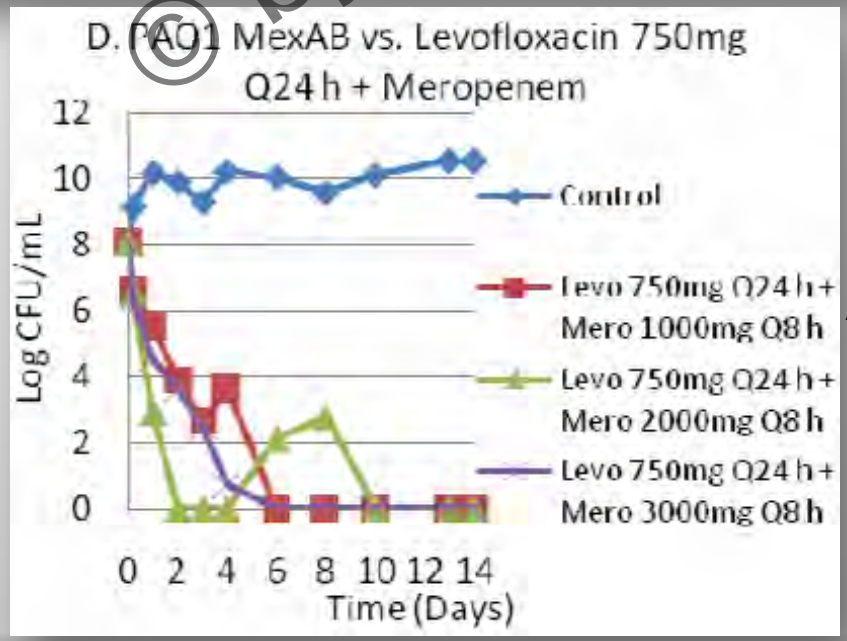


Bulik CC et al. AAC 2010;54:5209-13
Scheetz MH et al. Ann Pharmacother. 2006;40:2064-7
MacGowan A. JAC 2008;62 (suppl 1): i11-i16
Hawser S et al .IJAA 2012;39:490-5

Resistance Development - Combination

Meropenem/levofloxacin: Combination versus monotherapy for MexAB efflux pump-overexpressed PAO1 strain





A. Louie et al: AAC 2010, 54:2646-54

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Summary – What to do?

- Use antibiotics wisely – previous antibiotics reduce susceptibility
- Antibiotic dosage regimens influence probability of resistance emergence
- Optimize dosage if MIC unknown or expected to be elevated
- Monitor PK in high risk patients, TDM
- Re-evaluate duration of therapy frequently
- Use drug combinations

Hit hard and short (Hermann Spitzy, 1970)

International Society of Anti-Infective Pharmacology
Founded in 1991
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