Optimising therapy to minimise emergence of resistance

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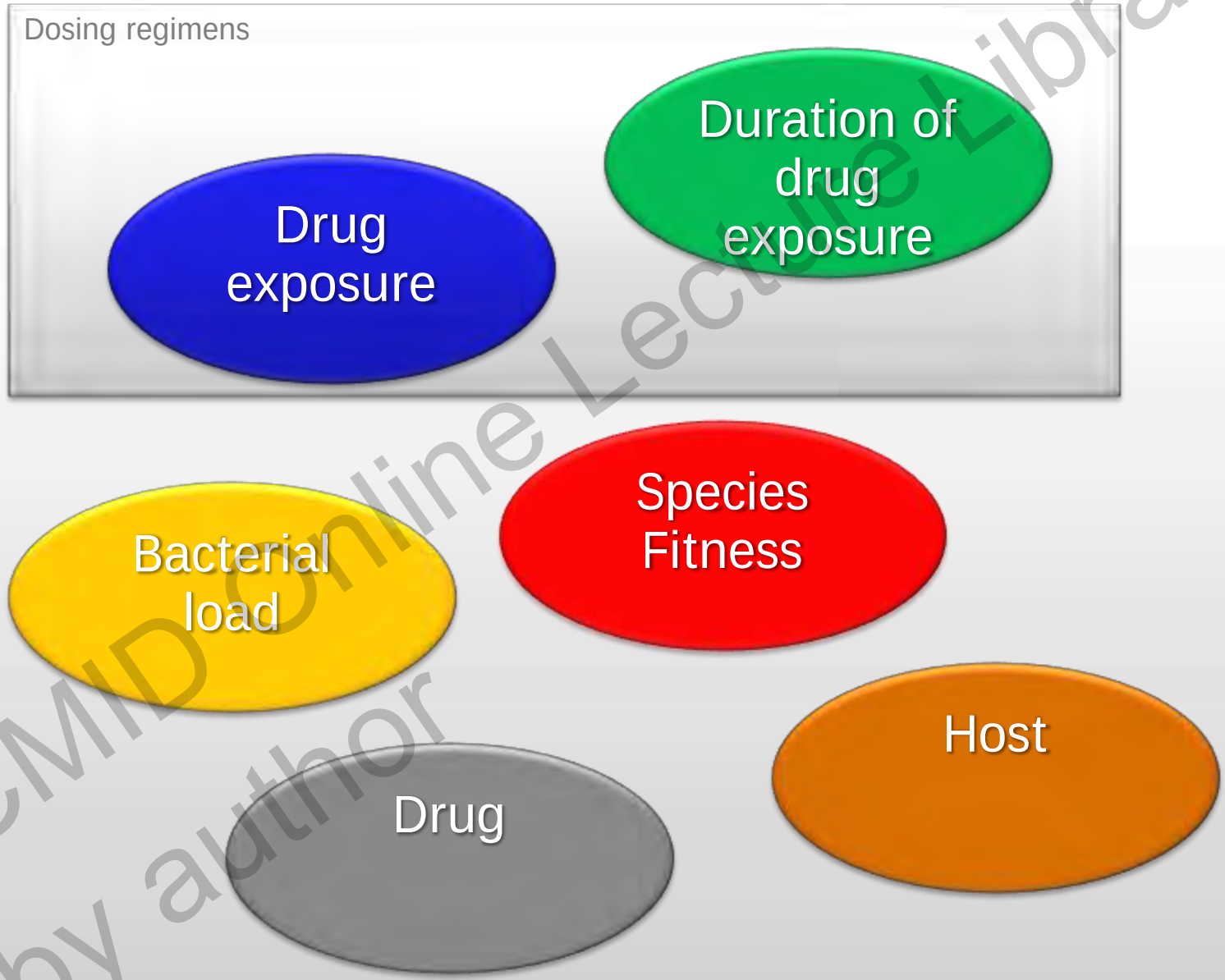
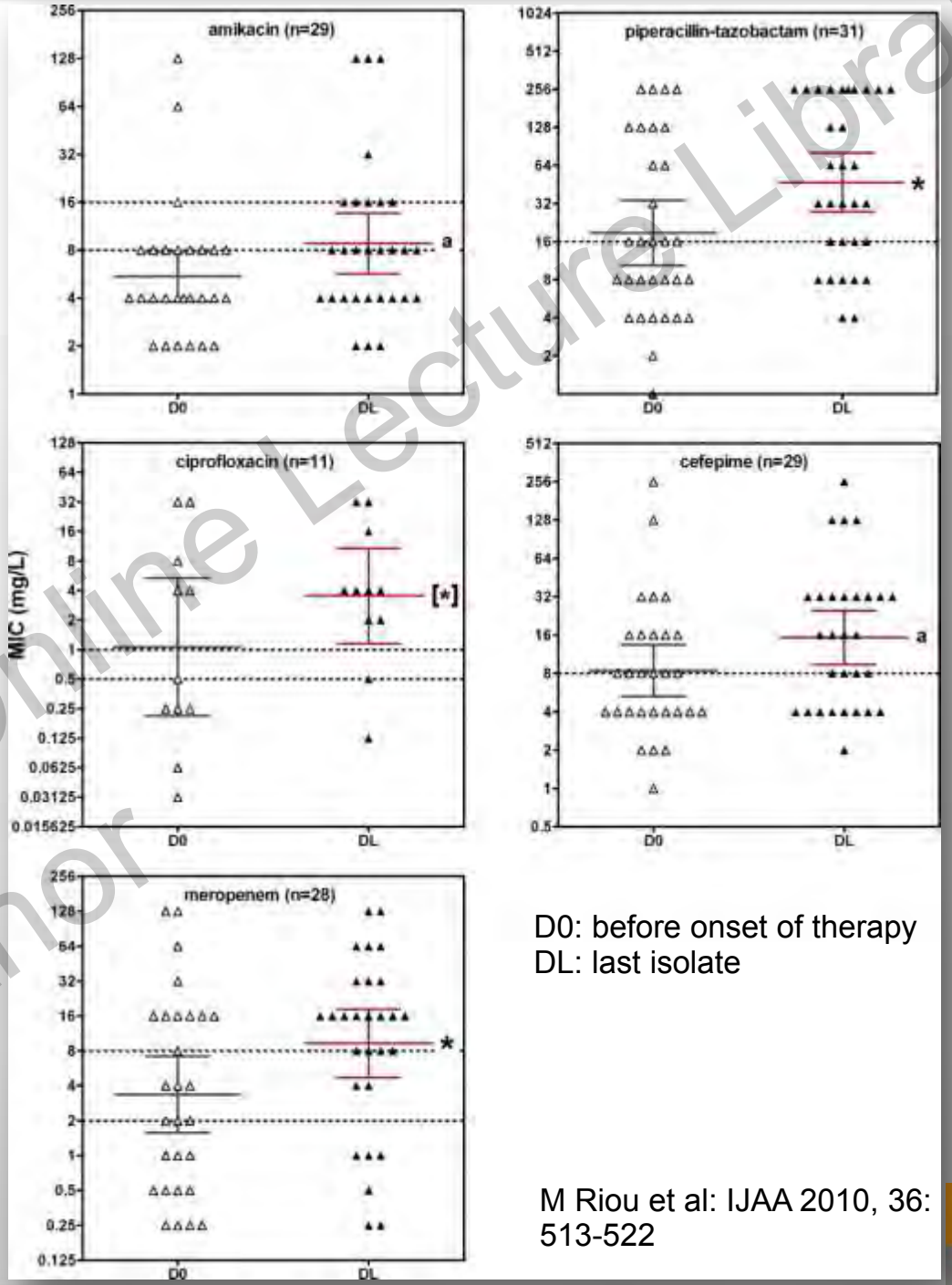
Emergence of resistance



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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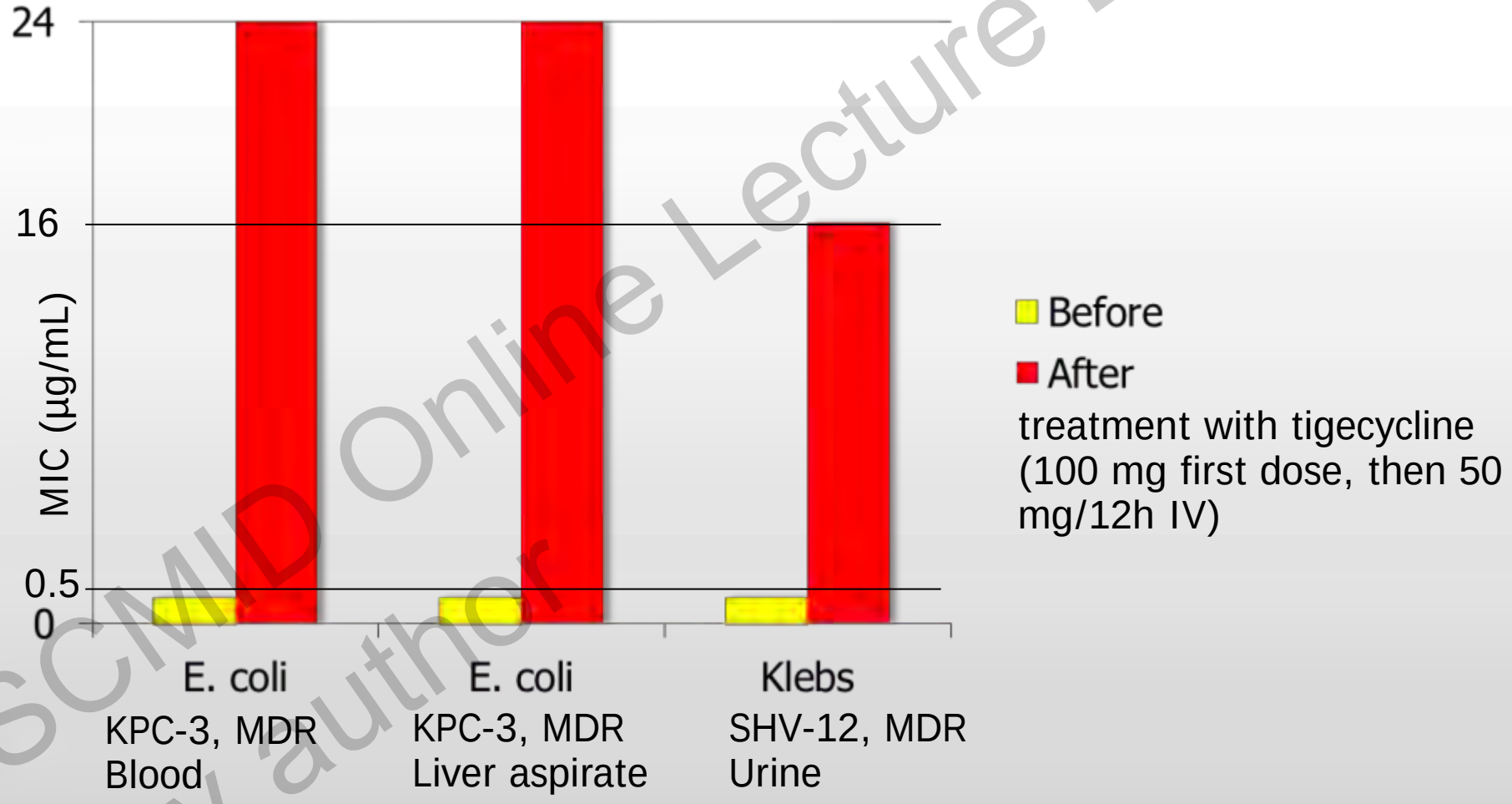
Emergence of Tigecycline Resistance

Clinical Emergence of Tigecycline Resistance in MDR K. pneumoniae and E. coli



treatment with tigecycline (100 mg first dose, then 50 mg/12h IV)

T. Spanu et al: AAC 2012, 56:4516-4518

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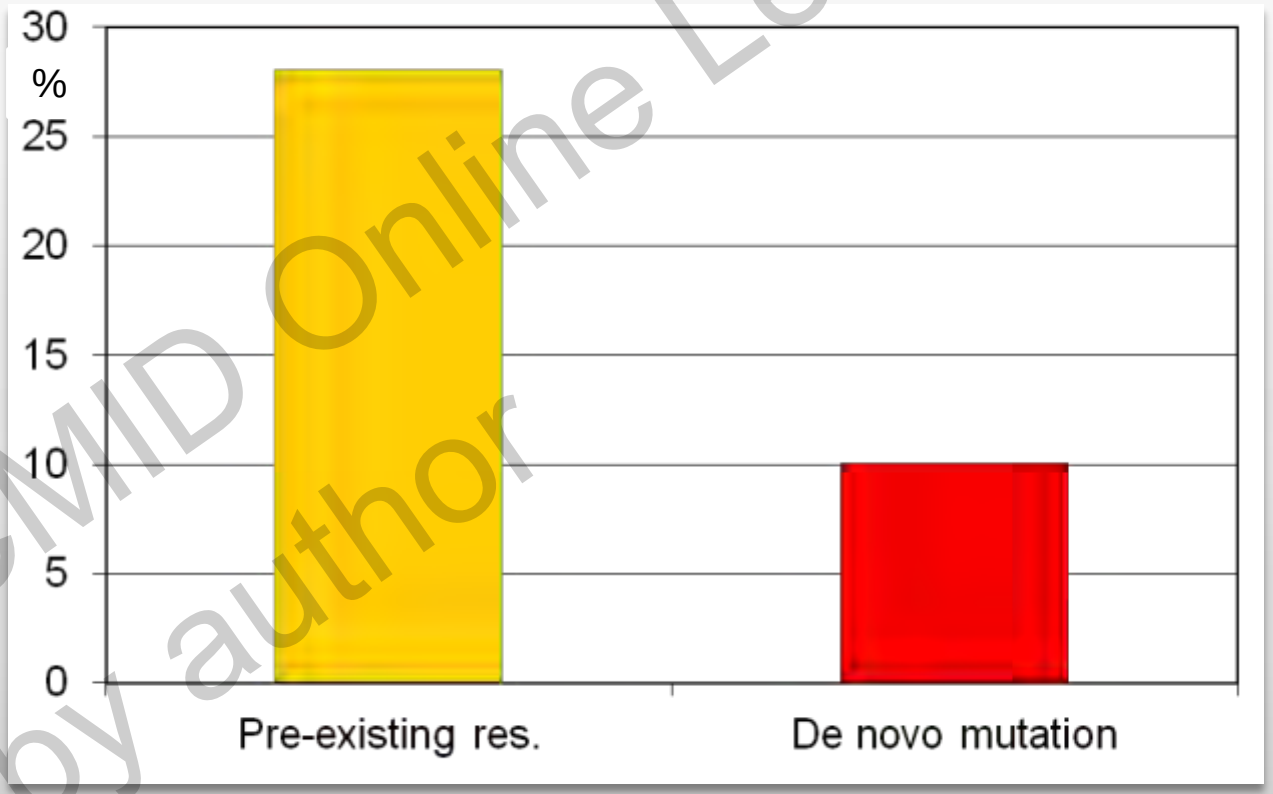
Emergence of resistance

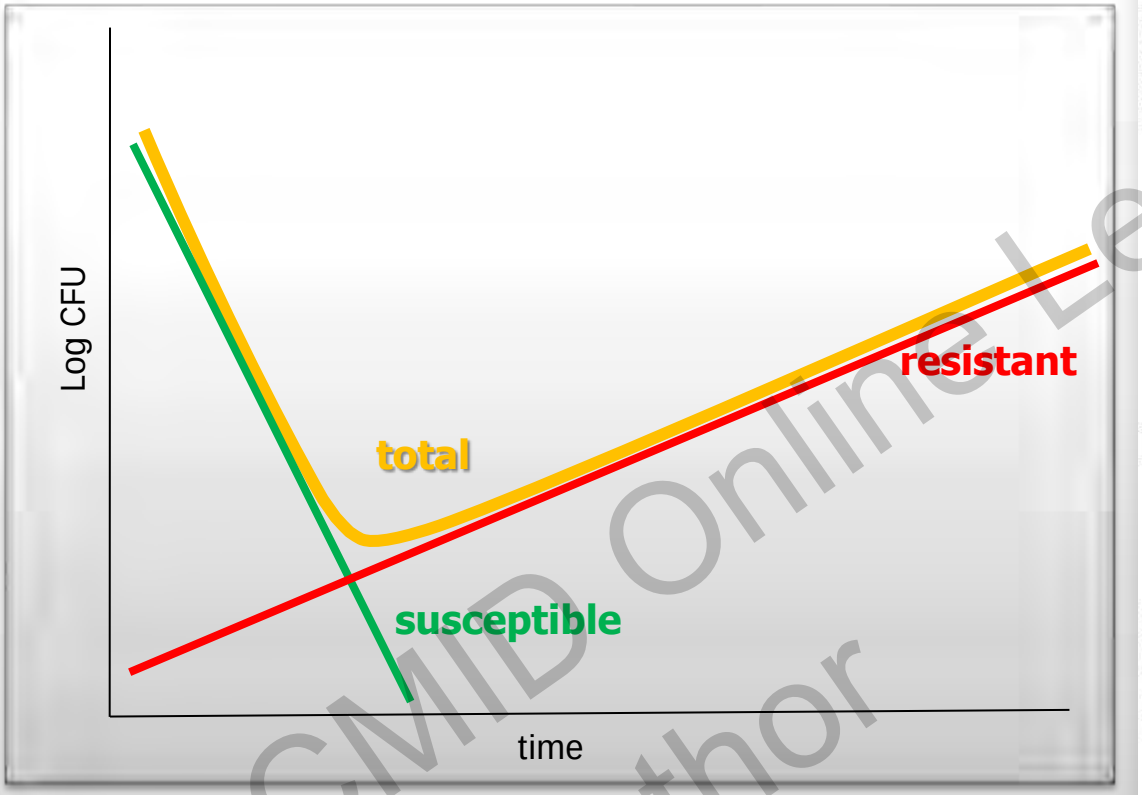
- Selection of
  - Pre-existing bacterial cells with reduced susceptibility
  - Bacterial cells with de novo mutations

Isolation of ciprofloxacin-resistant *E. coli* in hematological patients with ciprofloxacin prophylaxis (500 mg twice daily oral)



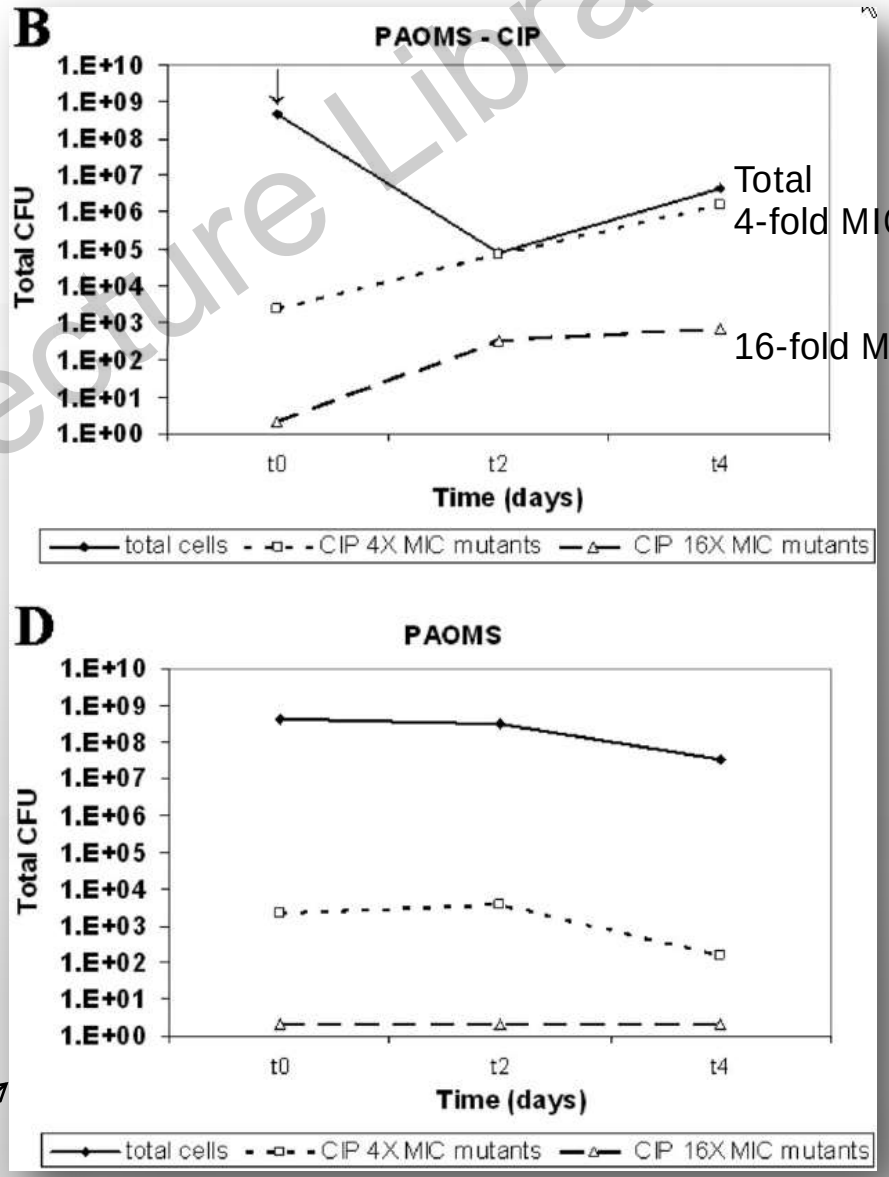
BC van Hees et al: JAC, 2011 66 (8): 1739-1744

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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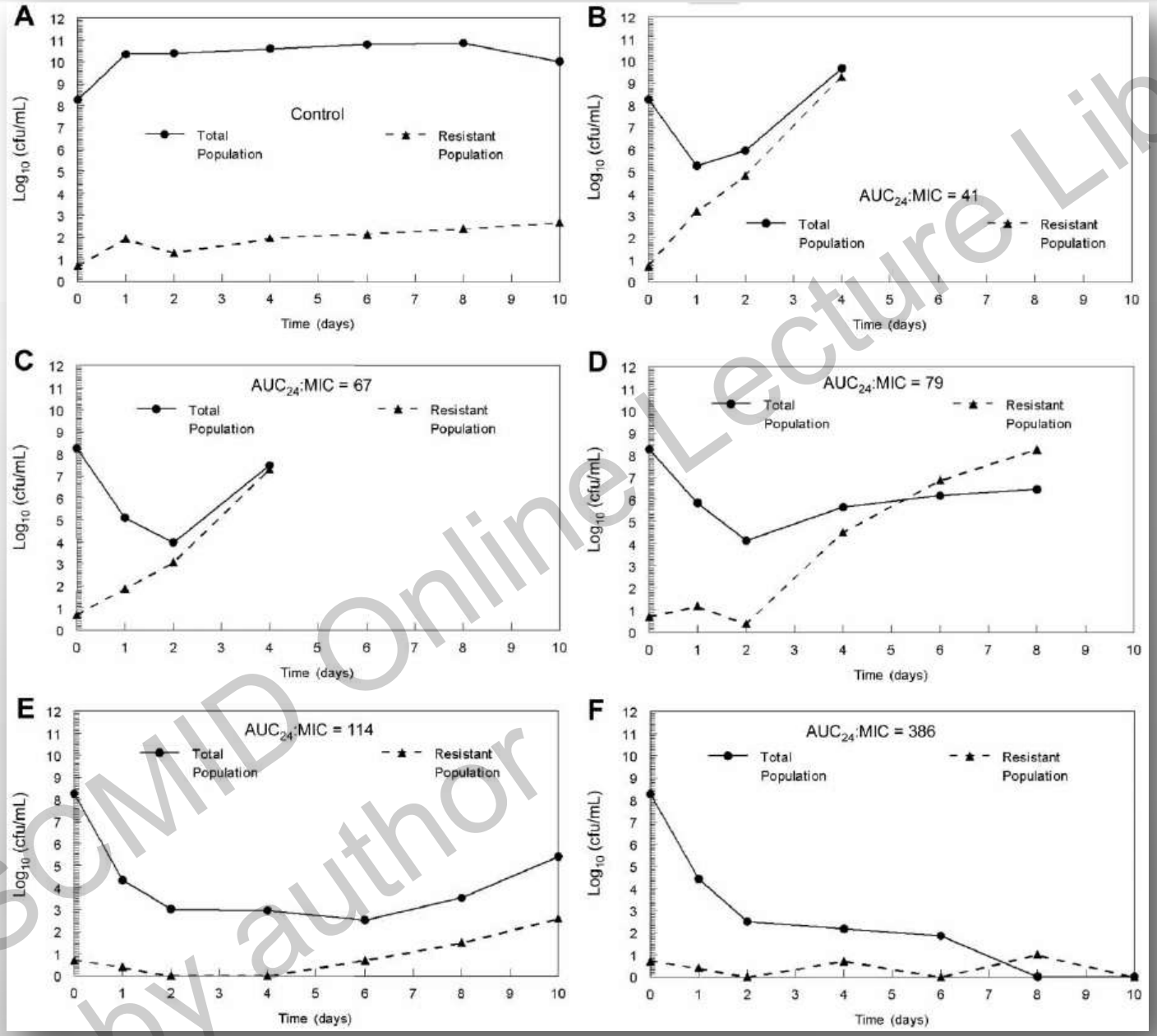
Exposure – resistance relationship



Garenoxacin
S. aureus
In vitro model

Duration of therapy !

V Tam et al: JID 2007;195:1818–27

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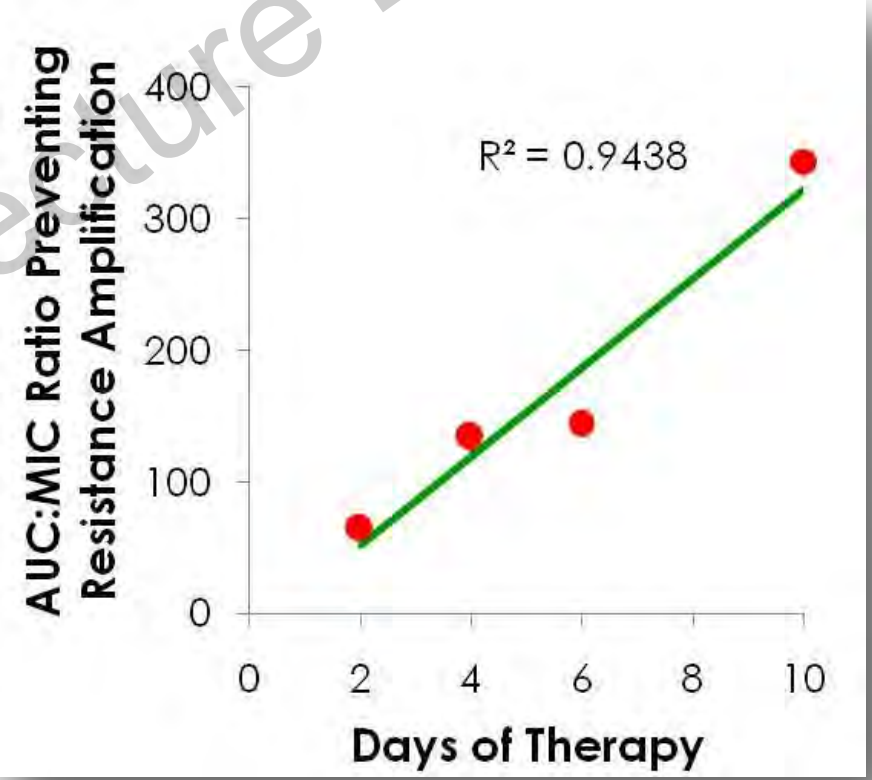
Resistance Development – Treatment Duration

Staph. aureus - Garenoxacin
*f*AUC/MIC 100

4 doses: susceptible population dominant, resistant subpopulation amplifying

>4 doses: resistant population exceeded the susceptible population at the end of therapy



G. Drusano et al. JID 2009, 199: 219
VH Tam et al: J Infect Dis 2007, 195:1818-27

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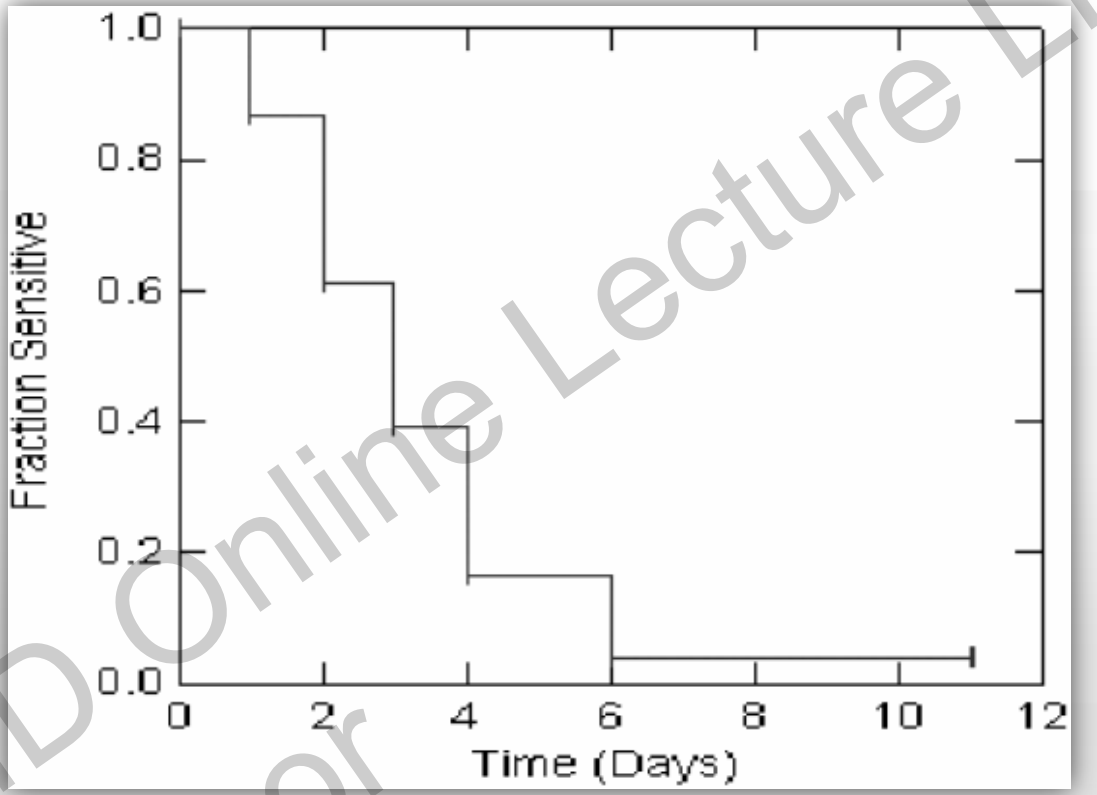
Resistance Development - Carbapenems

Pseudomonas: Time to emergence of resistance



PK/PD res: t>6xMIC
Doripenem 1g (4h inf), q8h: 50% (suppression of WT only)

A. Louie et al: AAC 2010, 54: 2638 - 2645

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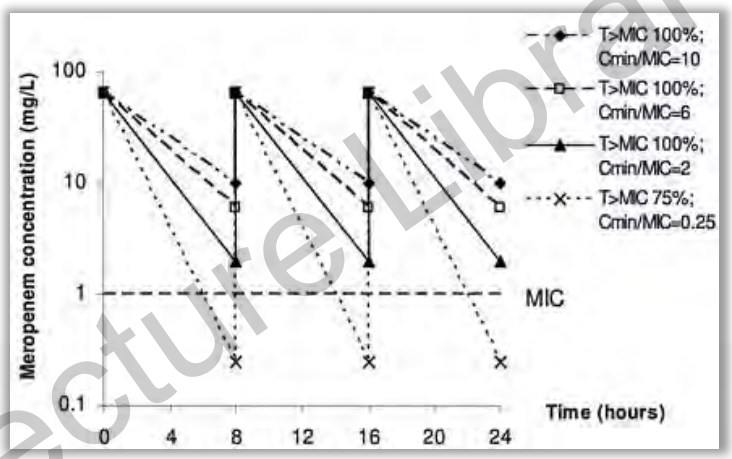
PK/PD - Selection of resistance

Meropenem - Pseudomonas

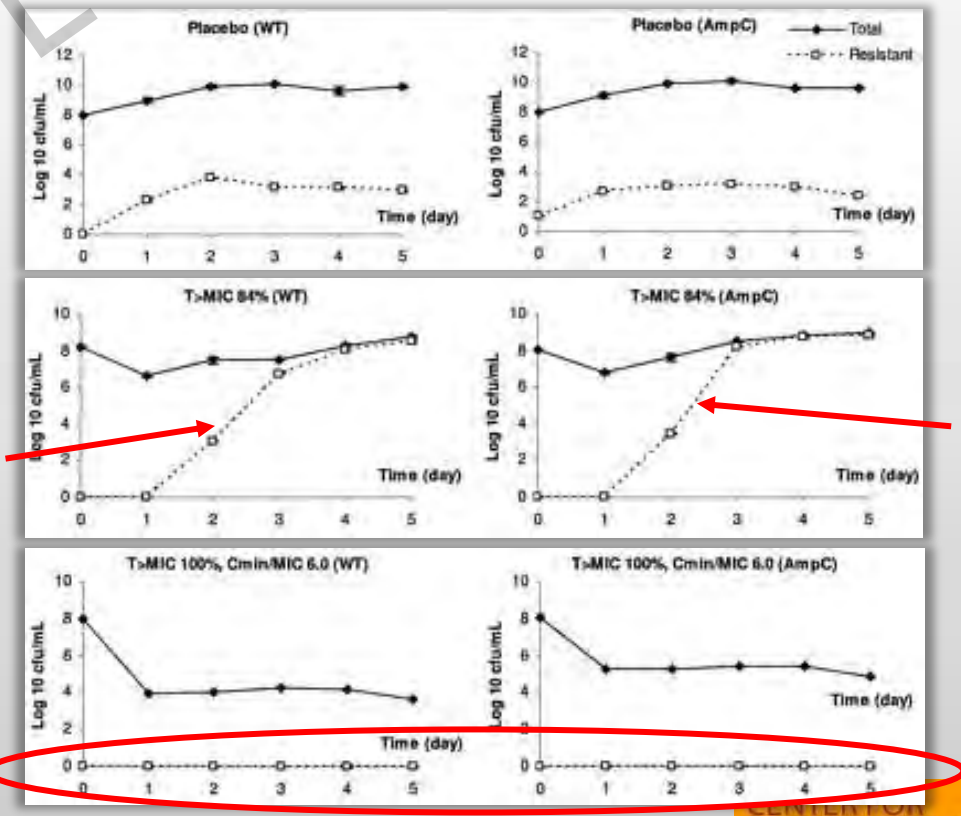
- P. aeruginosa: wild type + AmpC stably derepressed mutant (MIC = 1 mg/l)
- High inoculum, neutropenic



No selective pressure with placebo

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

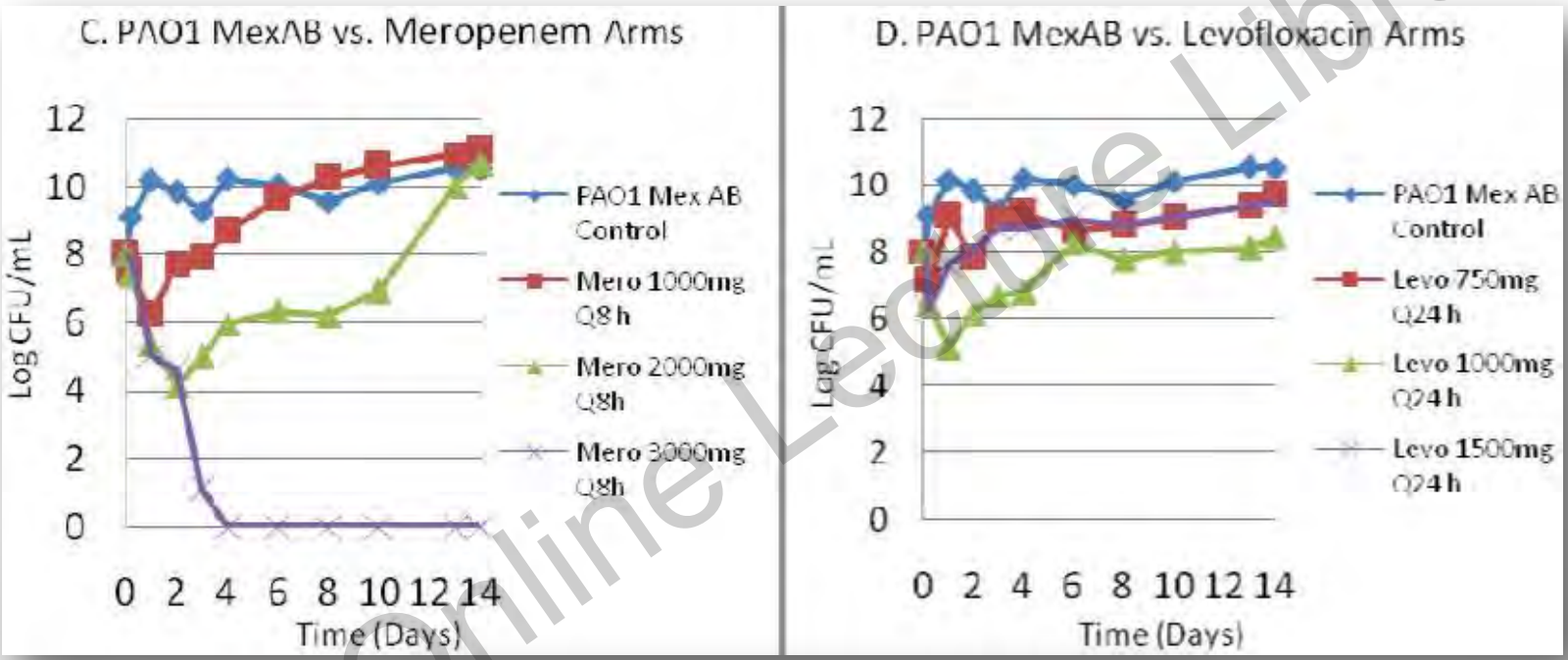
Optimized meropenem exposure **T>MIC=100%, C_{min}/MIC=6**: no growth

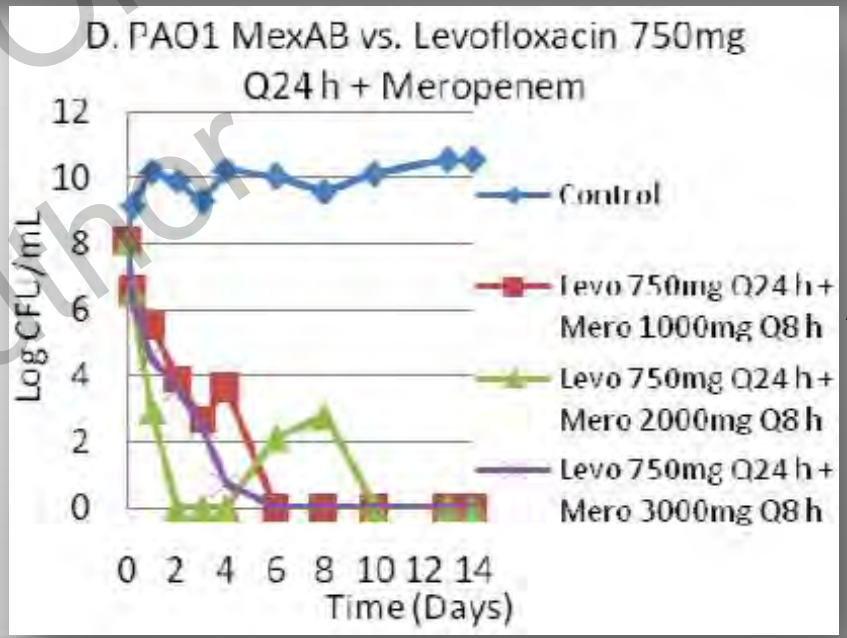


VH Tam et al: AAC 2005 (49), 12: 4920

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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Probability of Target Attainment

- Monte Carlo Simulation, P. aeruginosa, target AUC/MIC 157:
  (G. Drusano, 2012)
  - Ciprofloxacin 400mg iv q8h:
    PTA 62%, emergence of resistance 38%
  - Ciprofloxacin 200mg iv q12h:
    PTA 25%, emergence of resistance 75%

- Clinical studies:
  - Ciprofloxacin 400mg iv q8h:
    Emergence of resistance 33%
  - Ciprofloxacin 200mg iv q12h in nosocomial pneumonia
    Emergence of resistance 70-77%

C Peloquin et al: Arch Intern Med. 1989;149:2269-73
M Fink et al: AAC 1994 ; 38:547-557

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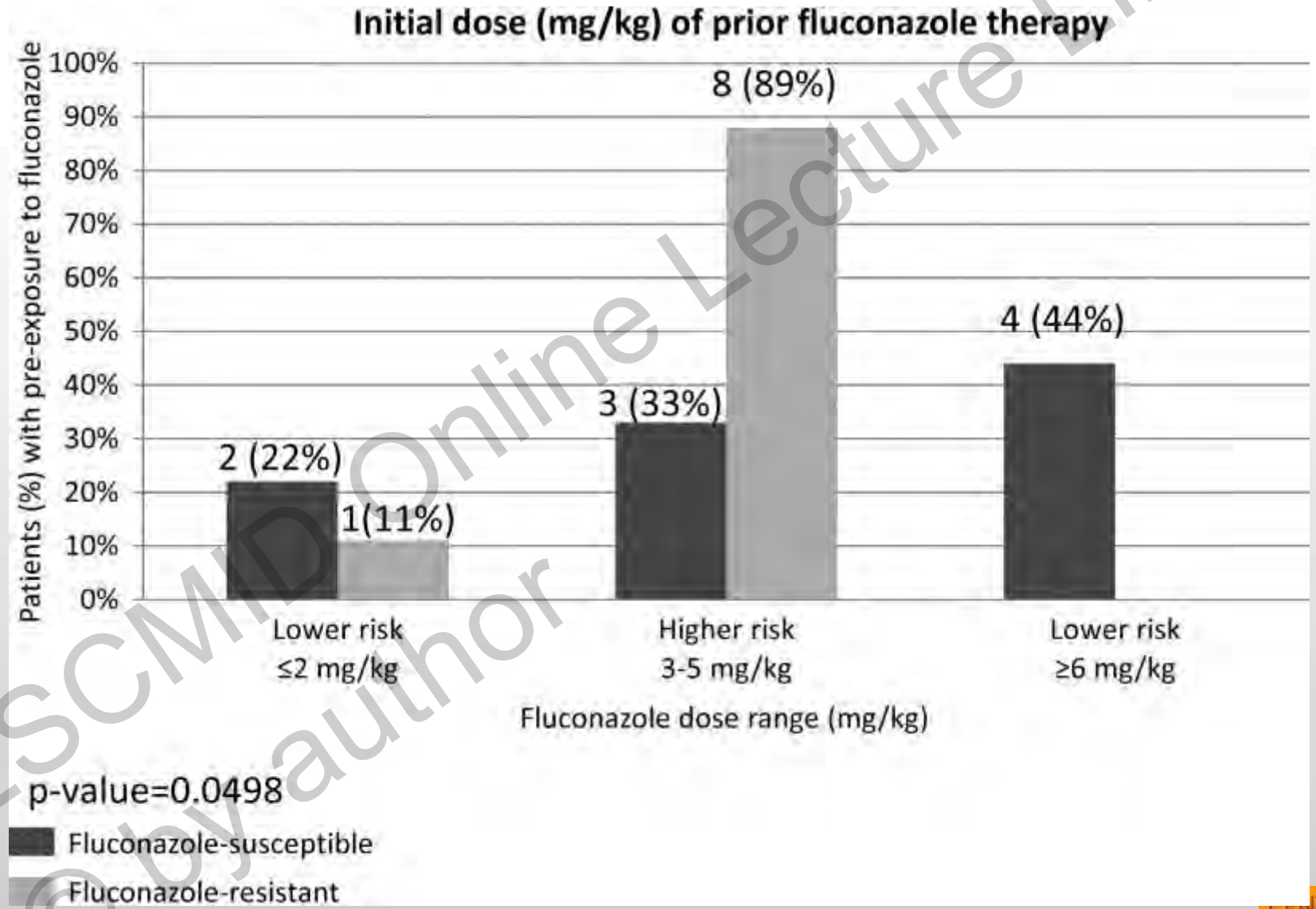
Exposure – Emergence of resistance

Initial doses during prior fluconazole therapy for patients with subsequent fluconazole-susceptible versus fluconazole-nonsusceptible candidemia

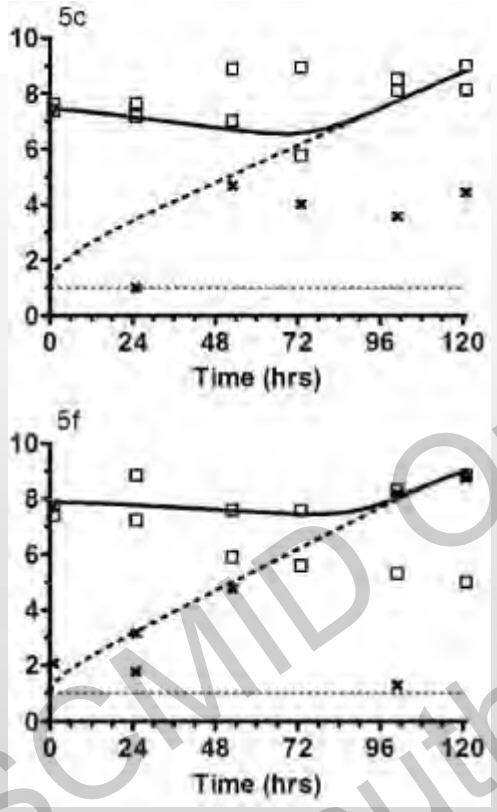


Shah D N et al. AAC 2012;56:3239-3243

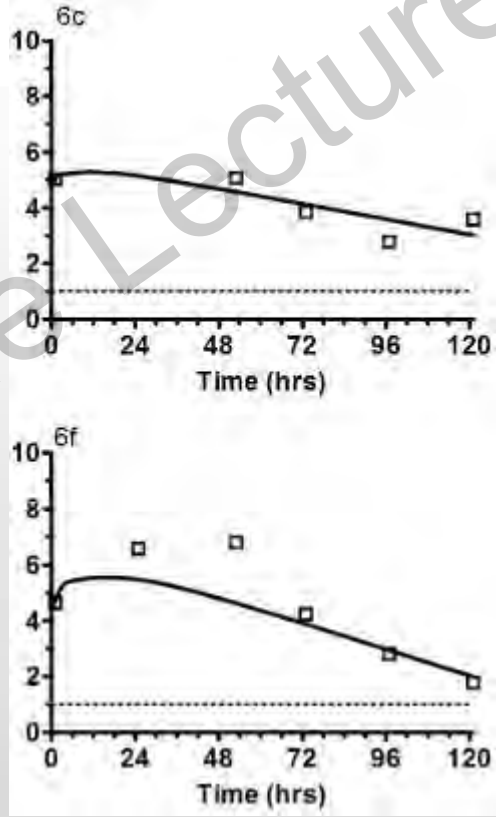
Bacterial densities

Piperacillin/ tazobactam – P. aeruginosa A01

High bacterial burden



Low bacterial burden



17g bolus

17g extended infusion

TW Felton et al: AAC, Sept 2013

Dose Optimisation – When?

- Critically ill patients with potentially decreased drug exposure
- Elevated MIC or risk for decreased susceptibility
- High bacterial burden
- Neutropenia

Summary – What to do?

- Use antibiotics wisely – previous antibiotics reduce susceptibility

- 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)

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