## Lipophilicity

- Obese subjects have a higher percentage of body fat
- The effect of body weight on volume of distribution depends on the lipophilicity of the drug

**Effects of obesity on volume of distribution**

Hydrophilic Drugs:

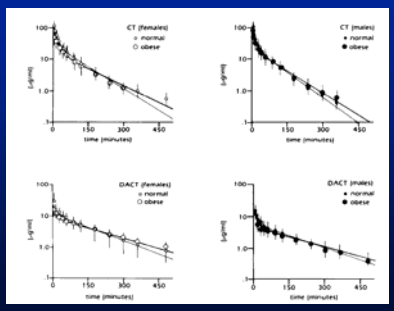
Little change in Vd, decrease in Vd/kg

Lipophilic Drugs:

Increase in Vd, increase in Vd/kg

Disposition of Cefotaxime and its Desacetyl Metabolite in Morbidly Obese Male and Female Subjects

Richard L. Yost and Hartmut Derendorf



*Ther Drug Monit 1986, 8 (2): 189-194*

## Body Weight

Gentamicin

Group I (average weight 55 kg)

Vd = 13 L or 0.24 L/kg

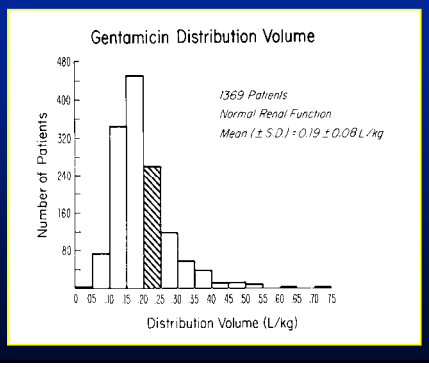
Group II (average weight 104 kg)

Vd = 19 L or 0.19 L/kg

**Uptake into excess body mass is about 40 % of uptake into lean body mass** Schwartz et al., 1976

## Gentamicin

**Volume of Distribution**




## Adjusted Body Weight (Dosing Weight)

**Aminoglycosides**

**ABW = IBW + 0.4·(TBW-IBW)**

ABW Adjusted Body Weight
IBW Ideal Body Weight
TBW Total Body Weight

## Aminoglycosides Vd for Obese and Non-Obese patients

| Reference | No. of subjects | Aminoglycoside | %IBW | Volume of distribution L/kg TBW | Volume of distribution L/kg IBW | Correction factor |
|---|---|---|---|---|---|---|
| Schwartz et al. | 6 | Gentamicin | 178* | 0.19 ± 0.03* | 0.34 ± 0.05* | 0.40 |
| | 8 | | 100 | 0.24 ± 0.05 | 0.24 ± 0.05 | |
| | 7 | Tobramycin | 181* | 0.23 ± 0.05* | 0.37 ± 0.06* | 0.40 |
| | 7 | | 100 | 0.30 ± 0.03 | 0.30 ± 0.03 | |
| Blouin et al. | 9 | Tobramycin | 225 | NR | 0.44 | 0.58 ± 0.22 |
| Bauer et al. | 7 | Amikacin | 255 | 0.17 ± 0.02 | 0.42 ± 0.10 | 0.38 ± 0.18 |
| Korsager | 17 | Gentamicin | 183 | NR | NR | 0.43 |
| | 10 | | 104 | | | |
| Sketris et al. | 30 | Gentamicin | 151* | 0.15 ± 0.04* | 0.23 ± 0.06* | 0.30 |
| | 30 | | 95 | 0.19 ± 0.06 | 0.19 ± 0.05 | |
| Bauer et al. | 12 | Gentamicin | >190 | 0.17 ± 0.04* | 0.41 ± 0.10* | 0.45 ± 0.24 |
| | 12 | | NR§ | 0.25 ± 0.04 | 0.25 ± 0.05 | |
| | 10 | Tobramycin | >190 | 0.19 ± 0.03* | 0.45 ± 0.08* | 0.37 ± 0.19 |
| | 10 | | NR§ | 0.26 ± 0.02 | 0.26 ± 0.03 | |
| | 8 | Amikacin | >190 | 0.18 ± 0.02* | 0.44 ± 0.09* | 0.42 ± 0.20 |
| | 8 | | NR§ | 0.26 ± 0.03 | 0.26 ± 0.03 | |
| Leader et al. | 100 | Gentamicin | 151* | NR | NR | 0.55 |
| | 100 | | 103 | NR | NR | |
| Treyner et al. | 534 | Gentamicin/tobramycin | >125 | 0.30 ± 0.12* | NR | 0.43 |
| | 1119 | | 75-124 | 0.35 ± 0.11 | NR | |

*Clin Pharmacokinet 2000, 38 (5): 415-426.*

## Weight Calculation in Obesity

| Measure | Formula |
|---|---|
| BMI | BMI = TBW/[Ht(m) × Ht(m)] |
| IBW (Devine) | IBW = 45.4 + [0.89 × (Ht(cm) − 152.4)] (+4.5 if male) |
| EBW | EBW = TBW − IBW |
| LBW (Janmahasatian) | Males: LBW = (9270 × TBW) / [6680 + (216 × BMI)]<br>Female: LBW = (9270 × TBW) / [8780 + (244 × BMI)] |
| FFM | Males: FFM = (TBW × 0.285) + [12.1 × Ht(m)$^2$]<br>Females: FFM = (TBW × 0.287) + [9.74 × Ht(m)$^2$] |
| ABW | ABW = IBW + [DWCF × (TBW − IBW)]<br>ABW = IBW + (DWCF × EBW) |
| PNW | Males: PNW = (TBW × 1.57) + (TBW × BMI × 0.0183) − 10.5<br>Females: PNW = [(TBW × 1.75) − (TBW × BMI × 0.0242) − 12.6 |
| BSA Dubois and Dubois | BSA = TBW$^{0.425}$ × Ht(cm)$^{0.725}$ × 0.007184 |
| BSA Mosteller | BSA = $\sqrt{}$ [Ht(cm) × Wt/3600] |

ABW, adjusted body weight; DWCF, dosing weight correction factor; EBW, excess body weight; FFM, fat-free mass; Ht(cm), height (in centimetres); Ht(m), height (in metres); IBW, ideal body weight; LBW, lean body weight; PNW, predicted normal weight; TBW, total body weight; Wt, weight.

*Curr Opin Infect Dis 2012, 25 (6): 634-649*

## Creatinine Clearance Calculations

| $CL_{CR}$ method | Equation |
|---|---|
| Cockcroft and Gault | $\frac{[(140 - age) \times TBW]}{(72 \times S_{CR})}$ |
| Modified Cockcroft and Gault | $\frac{[(140 - age) \times IBW]}{(72 \times S_{CR})}$ |
| Modified Cockcroft and Gault (C = 0.4) | $\frac{(140 - age) \times [IBW + C \times (TBW - IBW)]}{(72 \times S_{CR})}$ |
| Salazar-Corcoran | Males: $\frac{(137 - age) \times [(0.285 \times TBW) + (12.1 \times Ht^2)]}{(51 \times S_{CR})}$<br>Females: $\frac{(146 - age) \times [(0.287 \times TBW) + (9.74 \times Ht^2)]}{(60 \times S_{CR})}$ |
| Jelliffe | Males: $(\frac{100}{S_{CR}}) - 12$<br>Females: $(\frac{80}{S_{CR}}) - 7$ |

*Clin Pharmacokinet 2000, 38 (5): 415-426.*

## Body Weight

### Diazepam

Group I (average weight 61 kg)

Vd = 91 L or 1.5 L/kg

Group II (average weight 104 kg)

Vd = 292 L or 2.8 L/kg

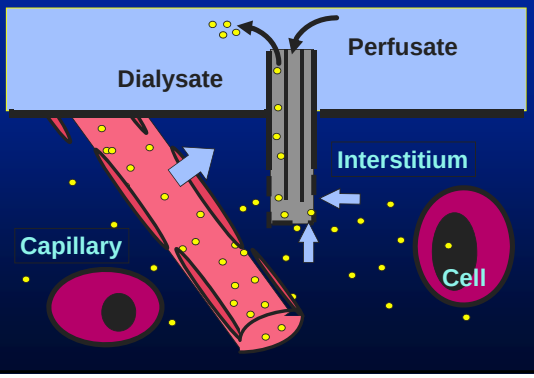
**Uptake into excess body mass is much higher than uptake into lean body mass**

## Antibiotics in Obesity

| | Hydrophilic antibiotics | Lipophilic antibiotics |
|---|---|---|
| Pharmacokinetics | • Generally have low volume of distribution.<br>• Are primarily cleared in kidneys.<br>• Have lower intracellular and tissue penetration. | • Generally have high volume of distribution.<br>• Are primarily cleared in the liver.<br>• Have higher intracellular and tissue penetration. |
| Changes in obesity | • Obesity has little effect on the antibiotic volume of distribution.<br>• Renal clearance is generally increased in obesity unless renal impairment is present. | • Obesity increases the antibiotic volume of distribution.<br>• Obesity have variable effects on hepatic clearance. |
| Dosing in obesity | Ideal or adjusted body weight is generally used for dosing[1]. | Total body weight is generally recommended for dosing[1]. |
| Examples of antibiotics | β-lactams (penicillins, cephalosporins, carbapenems)<br>Aminoglycosides<br>Vancomycin<br>Colistin | Fluoroquinolones<br>Macrolides<br>Tigecycline |

*Curr Opin Infect Dis 2013, 27 (2): 165-173*

## Microdialysis




Soft tissue penetration of cefuroxime determined by clinical microdialysis in morbidly obese patients undergoing abdominal surgery

April Barbour[a,1], Stephan Schmidt[a,1], W. Robert Rout[b], Kfir Ben-David[b], Olaf Burkhardt[c], Hartmut Derendorf[a,*]

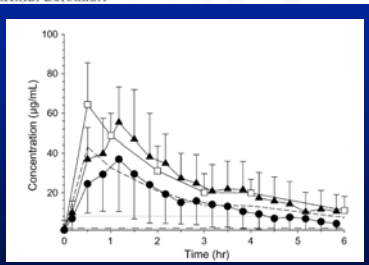
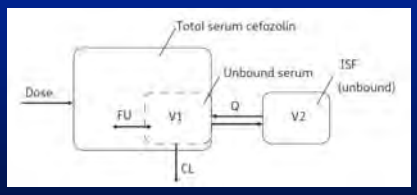



Figure: Mean concentration–time profile in plasma (square, solid line), free plasma (dashed line) and in the interstitial space fluid (free) of skeletal muscle (triangle, solid line) and subcutaneous adipose tissue (circle, solid line) of cefuroxime administered as a 1.5 g short-term intravenous infusion within 1 h of incision.

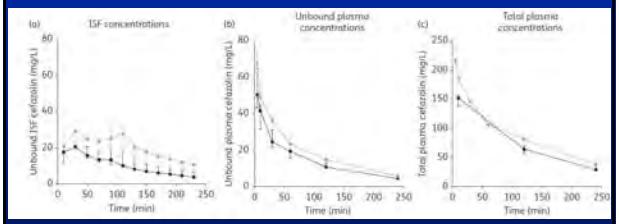
*Int J Antimicrob Agents 2009, 34: 231-235*

## Reduced subcutaneous tissue distribution of cefazolin in morbidly obese versus non-obese patients determined using clinical microdialysis

Margreke J. E. Brill[1,2], Aletta P. I. Houwink[3], Stephan Schmidt[4], Eric P. A. Van Dongen[3], Eric J. Hazebroek[5], Bert van Ramshorst[5], Véra H. Deneer[2], Johan W. Mouton[6] and Catherijne A. J. Knibbe[1,2]*




J Antimicrob Chemother 2014; 69: 715–723

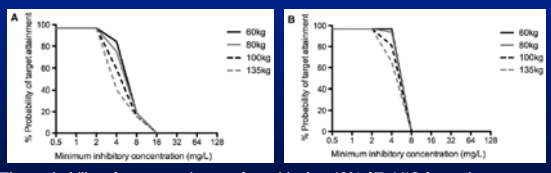



Observed cefazolin concentrations (median+IQR) in **morbidly obese (black symbols)** and **non-obese (grey symbols)** in (a) Subcutaneous ISF cefazolin. (b) Unbound plasma cefazolin. (c) Total plasma cefazolin.

J Antimicrob Chemother 2014; 69: 715–723

## Optimal Doripenem Dosing Simulations in Critically Ill Nosocomial Pneumonia Patients With Obesity, Augmented Renal Clearance, and Decreased Bacterial Susceptibility*

Jason A. Roberts, PhD[1,2,3]; Jeffrey Lipman, FCICM, MD[1,3]

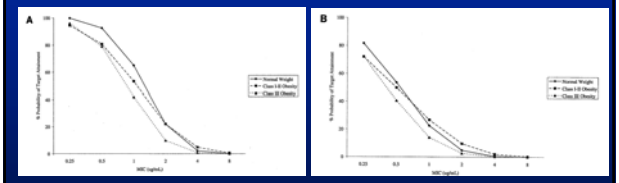



The probability of target attainment for achieving 40% *f* T>MIC for various simulated patient weights for 500 mg IV doripenem doses administered as **(A) 1-hr infusion** or **(B) 4-hr infusion** to patients with a glomerular filtration rate of 100 mL/min against a theoretical minimum inhibitory concentration range.

Crit Care Med 2013; 41 (2): 489-495

Comparative Pharmacokinetics and Pharmacodynamic Target Attainment of Ertapenem in Normal-Weight, Obese, and Extremely Obese Adults

M. Chen,[1,2] A. N. Nafziger,[1,2] G. L. Drusano,[3] L. Ma,[3] and J. S. Bertino, Jr.[1,2]*




Percent probability of attaining the **target of 20% (A)** or **40% (B) for fT >MIC** with a single 1-gram dose of ertapenem at MICs of 0.25, 0.5, 1, 2, 4, and 8 g/ml in normal-weight, class I-II obese, and class III obese groups.

*Antimicrob Agents Chemother 2006, 50: 1222-1227*

## Vancomycin PK Parameters in Obese and Non-Obese Patients

| Reference | No. of subjects | TBW (kg) | IBW (kg) | Volume of distribution L/kg TBW | Volume of distribution L/kg IBW | Clearance ml/min | Clearance ml/min/kg IBW | Clearance ml/min/kg TBW |
|---|---|---|---|---|---|---|---|---|
| Blouin et al | 6 | 165.7[a] | 63.5[a] | 0.26 ± 0.03 | 0.68 ± 0.07 | 187.50 ± 64.69 | 2.90 ± 0.61 | 1.11 ± 0.16 |
| | 4 | 74.6[b] | 72.7[a] | 0.39 ± 0.06 | NR | 80.78 ± 11.28 | 1.09 ± 0.07 | 1.09 ± 0.07 |
| Ducharme et al. | 108 | 94.3* | 59.7* | 0.56* | 0.89* | 74.4[b] | NR | NR |
| | 559 | 70.4 | 69.0 | 0.64 | 0.65 | 81.0 | | |
| Bauer et al. | 24 | 165 ± 46** | 63 ± 14 | 0.32 ± 0.05** | 0.83 ± 0.08** | 197 ± 77** | 3.1 ± 0.7** | 1.2 ± 0.2[b] |
| | 24 | 68 ± 6 | 64 ± 9 | 0.68 ± 0.24 | 0.64 ± 0.26 | 77 ± 22 | 1.0 ± 0.4 | 1.1 ± 0.3 |

a Calculated from data presented in original manuscript.
b Not significantly different from group immediately below ($p > 0.05$).
**IBW** = ideal bodyweight; **NR** = not reported; **TBW** = total bodyweight; * $p \leq 0.05$ compared with group immediately below; ** $p \leq 0.001$ compared with group immediately below.

*Clin Pharmacokinet 2000, 38 (5): 415-426.*

Vancomycin Pharmacokinetics in Normal and Morbidly Obese Subjects

ROBERT A. BLOUIN,[1] LARRY A. BAUER,[2]* DELWYN D. MILLER,[1] KENNETH E. RECORD,[1] AND WARD O. GRIFFEN, JR.[2]

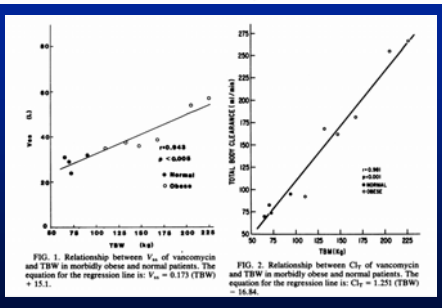


FIG. 1. Relationship between $V_{ss}$ of vancomycin and TBW in morbidly obese and normal patients. The equation for the regression line is: $V_{ss} = 0.173$ (TBW) + 15.1.

FIG. 2. Relationship between $Cl_T$ of vancomycin and TBW in morbidly obese and normal patients. The equation for the regression line is: $Cl_T = 1.251$ (TBW) − 16.84.

*Antimicrob Agents Chemother 1982, 21:575-580*

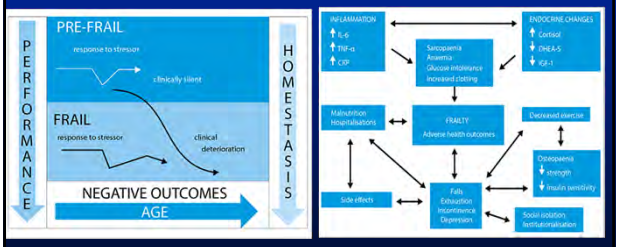
## Dose Adjustment in Obese Patients

| Class | Antibiotic | PK/PD-Index | Dosing Weight | Obese / Normal Doses |
|---|---|---|---|---|
| Aminoglycosides | Gentamicin | $C_{max}$/MIC | IBW | **540 mg/d / 380 mg/d** |
| Glycopeptides | Vancomycin | $AUC_{24h}$/MIC | TBW | **15-20 mg/kg / 5-7 mg/kg**LD |
| Penicillins | Piperacillin | T>MIC | TBW | **4.5-5 g q6h / 3-4 g q6h** |
| Cephalosporins | Cephazolin | T>MIC | TBW | **2 g q4-5 h / 1 g q4-5 h** |
| Carbapenems | Ertapenem | T>MIC | Unknown | **>1 g/day / 1 g/day** |
| Lipopeptides | Daptomycin | $AUC_{24h}$/MIC | TBW | **6 mg/kg** / 4 mg/ kg |
| Fluoroquinoliones | Ciprofloxacin | $AUC_{24h}$/MIC | ABW | **800 mg q12h / 400 mg q12hr** |

*Curr Opin Infect Dis 2012, 25 (6): 634-649*

## Frailty

"Is a state of 'weakness' where there is an increased vulnerability to adverse outcomes and where minor physiological stressors can lead to progressive deterioration".







*Continuing Medical Education 2013, 31 (10)*

## PK Changes in Frail Patients - Use of Antibiotics

- **Volume of distribution**
  - Prolonged half life
  - Increased plasma concentration
  - Changes in protein binding changes
- **Drug metabolism**
  - Half life changes for hepatically cleared drugs
  - Enzyme induction/inhibition
- **Renal drug elimination**
  - Half life changes
  - Drug accumulation in the plasma

Dose Optimization

*Drugs Aging 2007; 24 (4): 275-292*

## Dose Adjustment of Antibiotics in Patients with Pneumonia and Impaired Renal Functions

| Antibiotic | Renal function: | |
|---|---|---|
| | Moderately compromised (CLCr 30–50 mL/min) | Severely compromised (CLCr <30 mL/min) |
| Azithromycin | 500 mg q24 h | 500 mg q24 h |
| Cefotaxime | 2 g q6–8 h | 1 g q6–8 h |
| Ceftazidime | 1 g q8–12 h | 0.5 g q12 h |
| Cefepime | 1 g q8–12 h | 0.5 g q12 h |
| Ceftriaxone | 2 g q12–24 h | 2 g q12–24 h |
| Ciprofloxacin | 400 mg q8 h, 600 mg q12 h IV, 750 mg q12 h OS | 400 mg q8 h, 600 mg q12 h IV, 750 mg q12 h OS |
| Clarithromicin | 500 mg q12 h | 250 mg q12 h |
| Imipenem | 250 mg q6 h or 500 mg q8 h | 125 mg q6 h or 250 mg q8 h |
| Levofloxacin | 500 mg q24 h | 500 mg q48 h |
| Linezolid | 600 mg q12 h | 600 mg q12 h |
| Meropenem | 250 mg q6 h or 500 mg q8 h | 125 mg q6 h or 250 mg q8 h |
| Metronidazole | 500 mg q8 h | 500 mg q8 h |
| Moxifloxacin | 400 mg q24 h | 400 mg q24 h |
| Piperacillin/tazobactam | 3/0.375 g q6 h | 2/0.25 g q6 h |
| Teicoplanin | LD 12 mg/kg q12 h for 3 doses → 2–4 mg/kg q12 h | LD 12 mg/kg q12 h for 3 doses → 2–4 mg/kg q24 h |
| Vancomycin | LD 15 mg/kg → 7.5–15 mg/kg/die | LD 15 mg/kg → 5–7.5 mg/kg/die |

*Intern Emerg Med 2012, 7: 415-424*

## Challenges and Limitations

- **Obesity**
  - Difficult dosing extrapolation between healthy obese and sick obese patient population or critically ill patients
  - Dosing differences between different classes of obese patients
  - Type or location of infection may require change in dosing of the antibiotics
  - Development of resistance due to inadequate doing regimens
- **Frailty**
  - Resistant bacterial strains due to inadequate use of antibiotics
  - Previous antibiotic history
  - Polypharmacy and number of physiological changes

# Theuretzbacher - Optimising therapy to minimise emergence of resistance

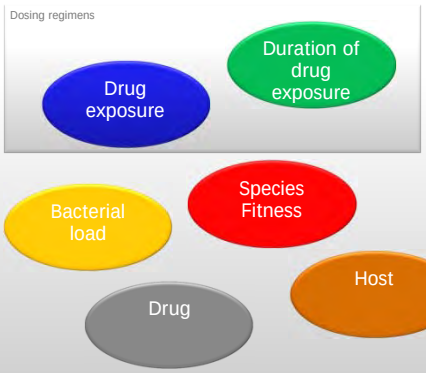
24th European Congress of Clinical Microbiology and Infectious Diseases 2014, Barcelona

## Optimising therapy to minimise emergence of resistance

U. Theuretzbacher – Center for Anti-Infective Agents, Vienna, Austria



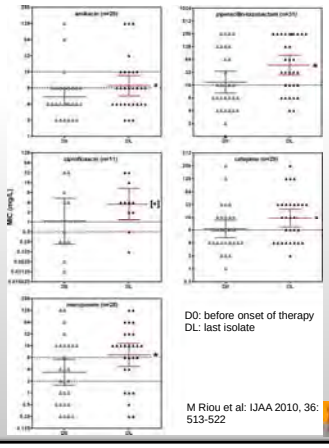
## Emergence of resistance






## Emergence of resistance

Pseudomonas HAP/VAP inf
Standard dosages in ICU

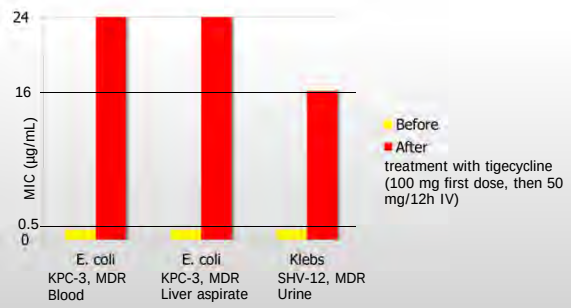


D0: before onset of therapy
DL: last isolate

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

## 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)

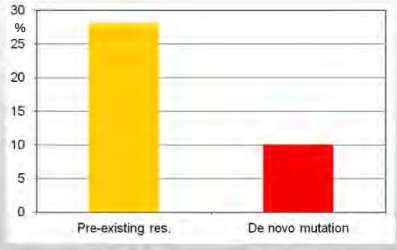
T. Spanu et al: AAC 2012, 56:4516-4518



## 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)



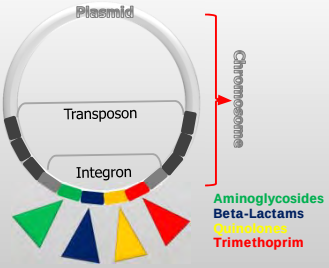

BC van Hees et al: JAC, 2011 66 (8): 1739-1744



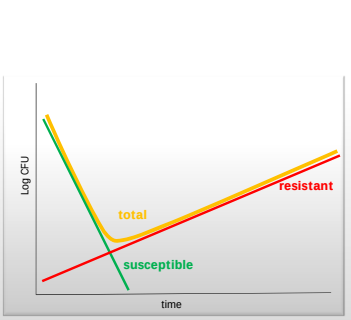
## Cross-resistance, Co-resistance

ESBL-producing Klebsiella

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

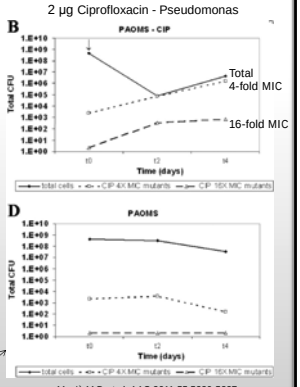


## Bacterial population analysis




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

2 µg Ciprofloxacin - Pseudomonas

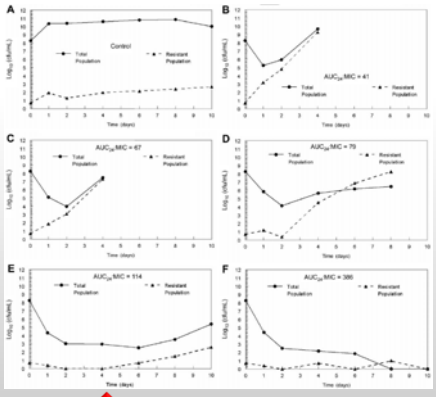



Control

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



## Exposure – resistance relationship




Garenoxacin
S. aureus
In vitro model

Duration of therapy !

V Tam et al: JID 2007;195:1818–27

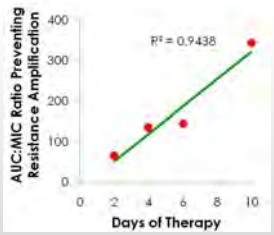


## Resistance Development – Treatment Duration

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

4 doses: susceptible population dominant, resistant subpopulation amplifying

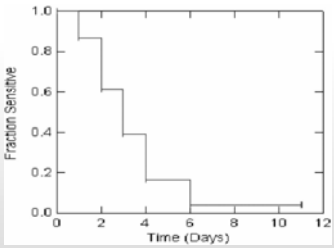
>4 doses: resistant population exceeded the susceptible population at the end of therapy




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

## Resistance Development - Carbapenems

Pseudomonas: Time to emergence of resistance




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

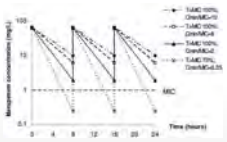
A. Louie et al: AAC 2010, 54: 2638 - 2645



## PK/PD - Selection of resistance

Meropenem - Pseudomonas

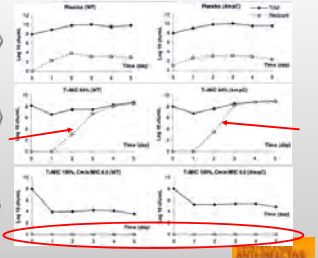
- P. aeruginosa: wild type + AmpC stably derepressed mutant (MIC = 1 mg/l)
- High inoculum, neutropenic



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

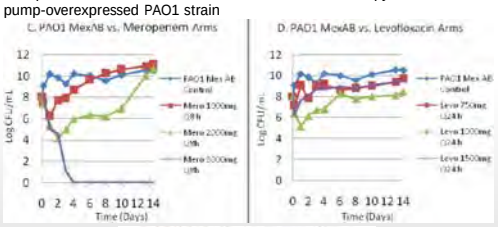


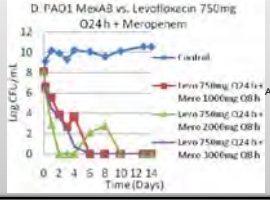
VH Tam et al: AAC 2005 (49), 12: 4920



## Resistance Development - Combination

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




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

## Probability of Target Attainment

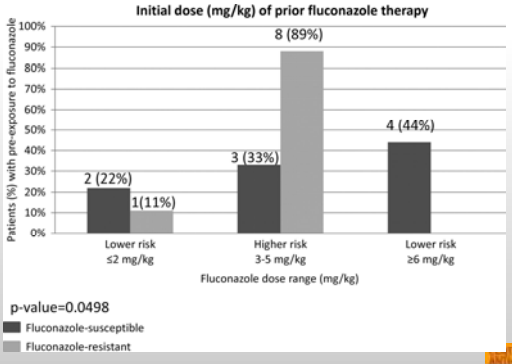
- Monte Carlo Simulation, P. aeruginosa, target AUC/MIC 157:
  (G. Drusano, 2012)
  - Ciprofloxacin 400mg iv q8h:
    PTA 62%, emergence of resistance 38%
  - Ciprofloxacin 200mg iv q12h:
    PTA 25%, emergence of resistance 75%
- Clinical studies:
  - Ciprofloxacin 400mg iv q8h:
    Emergence of resistance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



## Exposure – Emergence of resistance

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



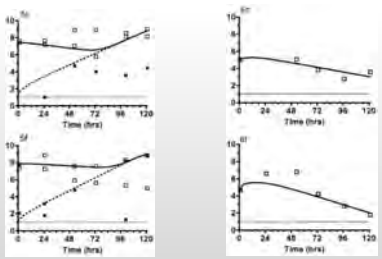

Shah D N et al. AAC 2012;56:3239-3243



## 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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