22nd ECCMID London, United Kingdom 31 March – 3 April 2012

Educational Workshop

EW02: Optimising treatment based on a pharmacodynamic approach: an interactive workshop using clinical cases

Arranged with the ESCMID PK/PD of Anti-Infectives Study Group (EPASG)

Convenors: **Ursula Theuretzbacher (Vienna, AT)**
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ESCMID EUROPEAN SOCIETY OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES

Aminoglycoside and Glycopeptide Dosing and Duration of Therapy

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Major Goal of Pharmacodynamics

Establish the **PK/PD TARGET** required for effective antimicrobial therapy

- identify which **PK/PD index** (T>MIC, AUC/MIC, peak/MIC) best predicts in vivo antimicrobial activity

- determine the **magnitude** of the PK/PD index required for in vivo efficacy (stasis, 1 or 2 log kill)

PK/PD Indices: Aminoglycosides

- **Animal Models:** AUC/MIC and Peak/MIC are important indices for efficacy of aminoglycosides.
  24-hr AUC/MIC ratio ≈100
  Peak/MIC ratio ≈8-10

Humans: AUC/MIC and Peak/MIC are important indices for 90% efficacy in serious Gram-negative bacillary infections (bacteremia and pneumonia).
24-hr AUC/MIC ratio > 110
Peak/MIC ratio >8-10

Smith et al. Clin Ther 2001; 23:1231; Kashuba et al Antimicrob Agents Chemother 1999; 43:623; Moore et al. J Infect Dis 155:93, 1987

Aminoglycoside Monotherapy

- 27 trials in patients with urinary tract infections
  Equal efficacy with competitors (β-lactams and fluoroquinolones)
- 9 trials in patients with non-urinary tract infections
  Higher rate of failure with aminoglycosides
- More nephrotoxic effects with aminoglycosides

Vidal et al. JAC 60:247, 2007

Expected Gentamicin Peak/MIC and AUC/MIC Values for Organisms with High MICs

PK/PD index	MIC	5 q 24h	7 q 24h	10 q 24h
Peak/MIC	1	14.7	20.5	29.3
AUC/MIC	1	55	77	110
EUCAST Breakpoint				
Peak/MIC	2	7.3	10.2	14.7
AUC/MIC	2	28	38	55
CLSI Breakpoint				
Peak/MIC	4	3.7	5.1	7.3
AUC/MIC	4	14	17	28

Combination vs Monotherapy for Pseudomonas Bacteremia

- Prospective observational study of 200 cases
- 91% received appropriate antipseudomonal antibiotics: 70% combination
  21% monotherapy
- Mortality: 27% combination therapy
  47% monotherapy
  (90% aminoglycoside alone)

Hilfe et al, Am J Med 87:540, 1989

Combination Therapy in Septic Shock

- **Retrospective, propensity-matched, cohort study of septic shock from ICU patients at 28 academic and community hospitals in 3 countries between 1996-2007.**
- **Matched 1223 patients each receiving monotherapy or combination therapy from 4662 eligible patients**

	ICU Mortality	Total Mortality	Ventilator Free Days
Monotherapy	37%	48%	10
Combination	29%	37%	17
p-value	0.0006	<0.0001	0.0008

Kumar et al Crit Care Med 2010; 38:1773

Combination Therapy in Septic Shock

- **Initial inappropriate antibiotic therapy more common with monotherapy than combination therapy (36% versus 22%)**
- **Addition of aminoglycoside to a β-lactam decreases initial inappropriate antibiotic therapy mainly for ESBL or AmpC Enterobacteriaceae and *P. aeruginosa* (33% to 8%) and coverage is wider than with fluoroquinolones**
- **Mortality significantly increased with initial inappropriate antibiotic therapy than with appropriate antibiotic therapy (52% vs 36%)**
- **Combination therapy a significant independent factor for reducing mortality in septic shock**

Micek et al Antimicrob Agents Chemother 2010; 54:1742
Martinez et al Antimicrob Agents Chemother 2010; 54:3590

Aminoglycoside Nephrotoxicity

- Megalin is a lipoprotein on the brush border of renal tubular cells that binds aminoglycosides and is important for uptake of these drugs by pinocytosis
- Animals deficient in megalin do not accumulate aminoglycosides in the kidney
- Binding to megalin by aminoglycosides is saturable
- Once-daily dosing results in less uptake in human kidneys than thrice-daily or continuous infusion; nephrotoxicity occurs later with once-daily dosing – usually after 5-7 days; with longer courses the difference between regimens becomes smaller

Nagai & Takano Drug Metab Pharmacokin 2004;19:159
Rougier F et al Antimicrob Agents Chemother 2003; 47:1010

Once-Daily Dosing of Aminoglycosides

- 45 studies, mostly prospective, in over 6500 patients comparing once-daily with multiple daily dosing
- Slight non-significant enhancement in efficacy
- Of 9 meta-analyses of different combinations of these 45 studies, 5 show a lower incidence of nephrotoxicity with once-daily dosing

Turnidge Inf Dis Clinics of N Amer 2003; 17:503

Optimizing Use of Aminoglycosides

- Once daily treatment of 5-7 mg/kg (gentamicin, tobramycin) or 15-20 mg/kg (amikacin) for short periods (5-7 days)
- For non-urinary tract infections: Target attainment inadequate for monotherapy against organisms with MICs > 0.5 mg/L (gentamicin, tobramycin) or 2.0 mg/L (amikacin)
- Addition of aminoglycoside to ß-lactam increases initial appropriate antibiotic therapy for resistant organisms, reduces early mortality in septic shock and increases ventilator/pressor-free days in ICU

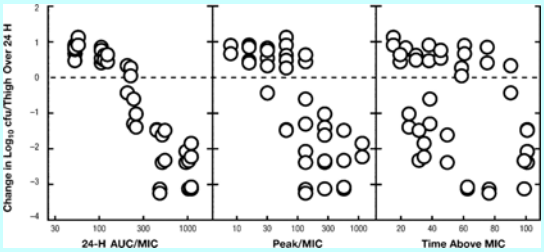
PK/PD of Glycopeptides in Animals (Vancomycin, Teicoplanin, Telavancin)

24-Hour AUC/MIC is the major PK/PD index correlating best with in vivo antimicrobial efficacy of glycopeptides

A few studies in non-neutropenic animals have also found good correlation with the Cmax/MIC index.

Ebert et al. 27th ICAAC, 1987
Knudsen et al Antimicrob Agents Chemother 2000; 44:1247
Hedge et al Antimicrob Agents Chemother 2004; 48:3034

Relationship between PK/PD indices for Vancomycin and Bacteriologic Efficacy against methicillin-susceptible *Staphylococcus aureus*



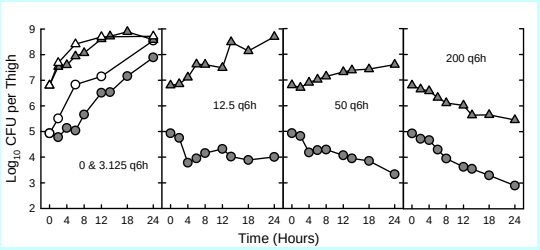
Ebert et al. 27th ICAAC, 1987
Rybak Clin Infect Dis 2006; 42:S35-S39

Glycopeptide PK/PD in Humans

- 108 patients with lower respiratory tract infections with *Staphylococcus aureus* treated with vancomycin
- Median time to eradication: 24-hr AUC/MIC <400 was > 30 days; 24-hr AUC/MIC >400 was 10 days (p=0.040)
- Odds Ratios for Clinical Success: 24-hr AUC/MIC >350 7.19 (1.91-27.3) (p=0.0036)
- Low penetration of vancomycin into ELF (15% of serum concentrations)

Moise-Broder et al Clin Pharmacokinet 2004; 43:925
Lamer et al Antimicrob Agents Chemother 1993; 37:281

Time Course of Antimicrobial Activity of Vancomycin against MRSA at Inocula of 10^5 and 10^7 in Opposite Thighs of the Same Neutropenic Mice



Lee et al Antimicrobial Agents Chemother 2012 (in press)

24-HR AUC/MIC for Stasis and 1 Log Kill with Vancomycin at Inocula of 10^5 and 10^7 against Multiple Strains of MRSA and *S. pneumoniae*

Inocula	*S. aureus*		*S. pneumoniae*	
	Total (Free) 24-Hr AUC/MIC			
	Stasis	I Log Kill	Stasis	1 Log Kill
Low 10^5	33.1 (24.5)	84.6 (62.6)	17.0 (12.6)	38.1 (28.2)
High 10^7	212 (157)	399 (295)	22.7 (16.8	39.1 (28.9)

Lee et al Antimicrobial Agents Chemother 2012 (in press)

Overall Probability of Achieving a 24-Hr AUC/MIC of 400 by Dose and MIC Versus Probability of a Nephrotoxic Event

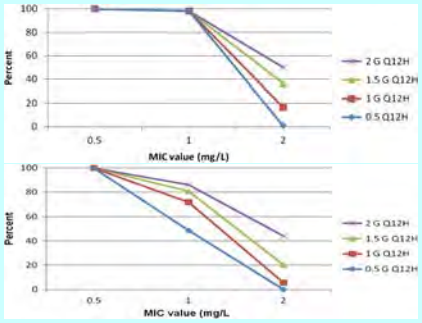
Vanco-mycin Dose IV q12h	AUC/MIC ratio ≥ 400 at MICs of			Nephrotoxic Event	
	0.5 mg/L (%)	1.0 mg/L (%)	2.0 mg/L (%)	Non-ICU (%)	ICU (%)
500 mg	57	15	0.7	3	10
1000 mg	90	57	15	6	16
1500 mg	97	79	38	9	25
2000 mg	98	90	57	14	34

Patel et al Clin Infect Dis 2011; 52:969

Probability of Achieving AUC/MIC Ratio ≥ 400

Trough 15-20 mg/L

Trough 10-15 mg/L



Patel et al Clin Infect Dis 2011; 52:969

Outcome in MRSA Bacteremia

- Single-center retrospective analysis of 320 patients with complicated MRSA bacteremia who received vancomycin for >72h from Jan 2005 to Apr 2010
- Cmin (before 4th dose) and calculated 24-Hr AUC (by dividing dose by clearance) were correlated with outcome
- Initial Cmin <15 mg/L and Etest MIC>1 were independent predictors of failure
- Cart partition analysis: Failure
  - 24-hr AUC/MIC ratios ≥ 421 48.6%
  - 24-Hr AUC/MIC ratios < 421 61.2% P= 0.038

Kuller et al Clin Infect Dis 2011; 52:975

Vancomycin Trough Concentration and Poor Outcomes

Trough (Cmin) Values	Vancomycin Failure (%)	P vs REF	Nephrotoxicity (%)	P vs REF
<10 mg/L	46/70 (66%)	0.001	10/65 (15%)	0.682
10-14.9 mg/L	52/90 (58%)	0.016	13/76 (17%)	0.476
15-20 mg/L	34/86 (39%)	REF	10/77 (13%)	REF
>20 mg/L	31/62 (50.0%)	0.206	17/62 (27%)	0.032

Nephrotoxicity was significantly higher in vancomycin failures (20.2% vs 10.5%)
Nephrotoxicity higher with concomitant aminoglycosides (19.6% vs 11.2%)

Outcome in Complicated MRSA Bacteremia and Endocarditis

- Single-center retrospective analysis of 50 patients with complicated MRSA bacteremia or endocarditis treated with vancomycin from Jul 2006 to Jun 2008
- CART Partition Analysis:

	Mortality	
24-Hr AUC/MIC <211	63%	
24-Hr AUC/MIC ≥211	19%	P = 0.02

- 24-hr AUC/MIC <211 and the APACHE II score were both independent predictors of failure by logistic regression

Brown et al Antimicrob Agents Chemother 2012; 56:634

Continuous Infusion of Vancomycin

- Vancomycin has concentration-independent bactericidal activity
- Continuous infusion could promote continual maximal bactericidal activity during therapy
- Most studies have target serum concentrations of 20-25 mg/L
- This would result in 24-hr AUCs of 480-600 mg-hr/L and would provide 24-hr AUC/MIC values above 400 for strains with MICs of 1 mg/L or less

Cataldo et al J Antimicrob Chemother 2012; 67:17

Continuous Versus Intermittent Infusion of Vancomycin

- Systemic review and meta-analysis of 1 randomized controlled trial and 5 observational studies
- Overall mortality was not different between the two groups
- Continuous infusion resulted in a significantly lower risk of nephrotoxicity than with intermittent infusion
- Two studies reported a 12-14% lower vancomycin exposure (mean AUCs) with continuous infusion

Cataldo et al J Antimicrob Chemother 2012; 67:17

PK/PD Targets for Teicoplanin

- A Cmin target of 13 mg/l and a 24-Hr AUC target of 750 mg-hr/L were associated with 90% eradication of MRSA
- In 70 patients with *S. aureus* bacteremia treated with teicoplanin, a mean Cmin ≥ 10 significantly increased the probability of a successful outcome
- A systematic review and meta-analysis of teicoplanin versus vancomycin showed no significant differences in clinical or microbiologic failure
- Teicoplanin was associated with significantly less nephrotoxicity and red man syndrome

Kanazawa et al J Infect Chemother 2011; 17:297
Harding et al J Antimicrob Chemother 2000: 45:835
Svetitsky et al Antimicrob Agents Chemother 2009; 53:4069

Duration of Therapy with Glycopeptides

Infection	Duration of Therapy
Complicated SSTI	1-2 weeks
Pneumonia	1-3 weeks
Uncomplicated bacteremia	2 weeks
Complicated bacteremia	4-6 weeks
Endocarditis	6 weeks
Osteomyelitis	8 weeks
Septic arthritis	3-4 weeks

- Relapse in complicated bacteremia much more frequent after 14 days of therapy than after 30 days of therapy

Liu et al Clin Infect Dis 2011; 52:285
Asgeirsson et al J Infect 2011; 62:339

Factors Affecting MRSA Eradication

Specific genotypic and phenotypic factors correlate with duration of MRSA bacteremia

		Median Time to Clearance	
Agr genotypes:			
	agr III	3 days	
	agr I	10.5 days	p=0.001
	agr II	15 days	
In vitro killing			
	< 2.5 log killing	>10.5 days	
	≥ 2.5 log killing	6.5 days	p=0.025

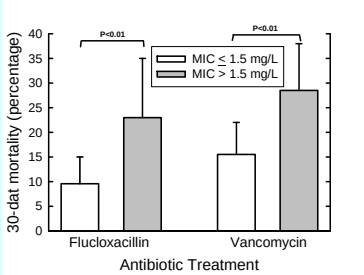
Moise et al Antimmicrob Agents Chemother 2007; 51:2582
Moise et al J Infect Dis 2010; 201:233

Vancomycin and Flucloxacillin Outcomes in MSSA and MRSA Bacteremia

- Multicenter observational cohort of patients with MSSA and MRSA bacteremia treated with vancomycin from Jan 2007 to Nov 2008. Each vancomycin-treated MSSA or MRSA case was matched with the next MSSA case treated with flucloxacillin (266 patients with each drug).
- Etest used for vancomycin MICs; no positive correlation between vancomycin and oxacillin MICs.
- 30-day mortality used to measure outcome
- Multivariate analysis showed a significant relationship between 30-day mortality and high vancomycin Etest MIC for patients treated with either drug

Holmes et al Clin Infect Dis 2011; 204:340

30-Day Mortality Versus Vancomycin MIC



High vancomycin MIC could reflect some unidentified host or organism factor that affect treatment outcomes

Holmes et al Clin Infect Dis 2011; 204:340

Mortality and Vancomycin MICs > 1.5 mg/L

- **Systemic review and meta-analysis of 22 studies**
- **Mortality significantly higher in patients infected with MRSA strains with a vancomycin MIC > 1.5 mg/L**
- **Difference predominately driven by bloodstream infections**
- **No data yet to support better survival rates with alternative antibiotics**

Van Hal et al Clin Infect Dis 2012; 54:755

Thank you for your attention

Nijmegen Institute for Infection, Inflammation & Immunity

Optimizing treatment on the ICU

Johan W. Mouton MD PhD FIDSA

EPASG/ISAP Workshop 2012

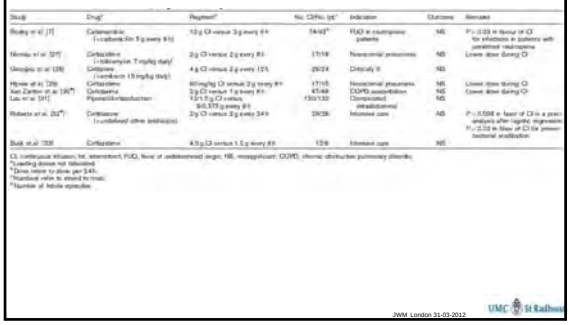
Trauma Patient

- 21 years old
- Hit a tree
- On the ICU since three days
- Suspicion of VAP
- No significant culture results at this moment
- Treatment with BSC is started

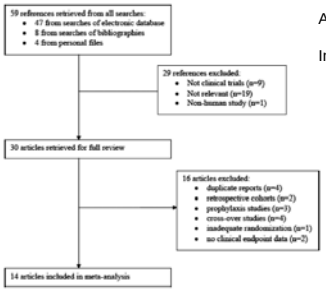
- Ceftazidime is started by continuous infusion, 3 gram/day. The reasons for CI are :

  it has been demonstrated to be more efficaceous?

Results of Clinical Trials
Continuous infusion



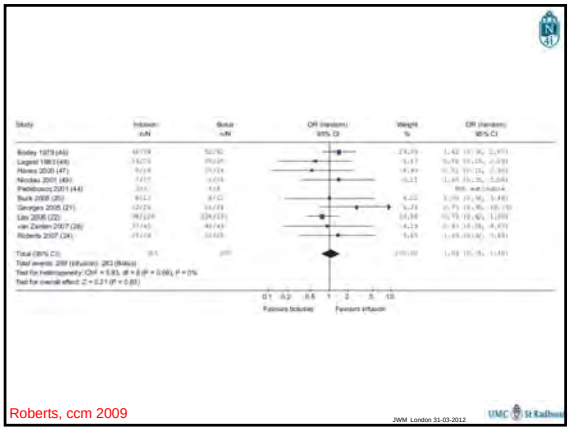
Metaanalysis



Acute infections only

Included extended infusion

Roberts, ccm 2009

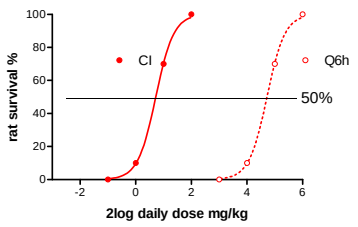


Roberts, ccm 2009

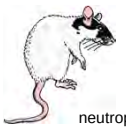
So why do we think it is more efficaceous?

a. Because of pharmacodynamic principles
b. Because extensive studies in animals have shown a clear benefit
c. Because extensive studies in animals AND in vitro have shown a clear benefit
a. Because everyone tells us so, so it must be true

Rat survival : 4 days Continuous Infusion vs Q6h



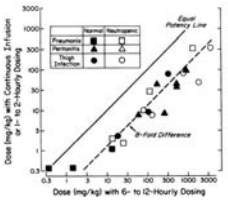
Regimen	PD50 mg/kg
CI	1.52
Q6h	24.37



neutropenic

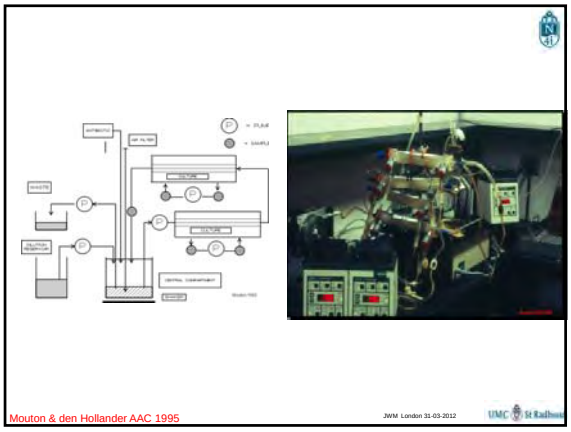
Adapted from Roosendaal AAC 1986

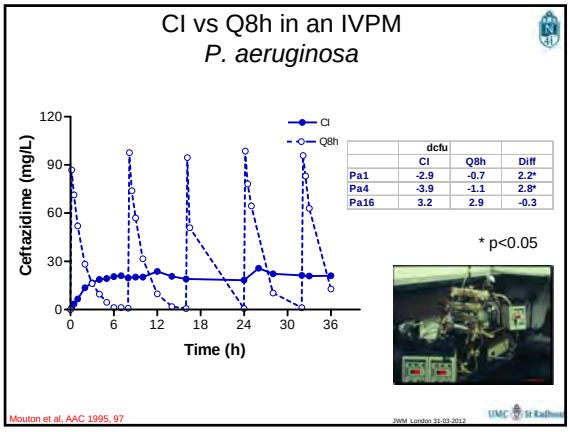
Effect of longer vs shorter intervals or CI in animals



- Effect of larger dosing intervals vs CI or q1 or 2h
- 8 fold difference in potency

Craig and Ebert AAC 1992





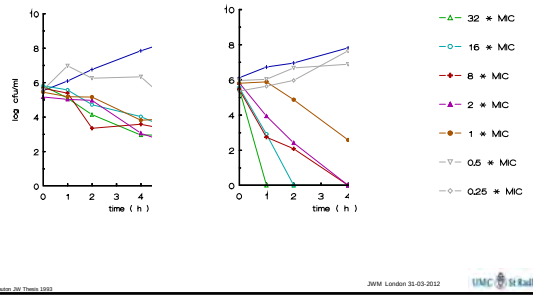
A concentration independent antibiotic means that:

a. Independent of the concentration, the drug should work

b. High concentrations provide no benefit

JWM London 31-03-2012

Patterns of activity:
Kill curves of P. aeruginosa



Mouton JW Thesis 1993

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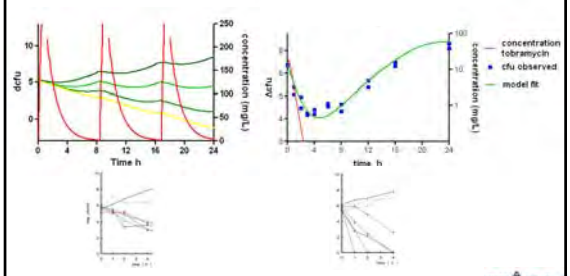
Beta-lactam | Aminoglycoside



Mouton et al, ICAAC 1997, ECC 1999

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The literature states that one needs at least
40% T>MIC for a clinical cure by beta-lactams because:

a. Human trials have shown this.
b. Extensive animals have shown this
c. a and b are true
d. Other reasons

JWM London 31-03-2012

Predicted *f*T>MIC needed for in vivo static effect -- Mice

regimen	Mouse[1] mg/kg	%*f*T>MIC
q2	2.12	37.3
q3	4.60	38.1
q4	9.29	37.6
q6	35.6	36.5
q8	129.7	35.7
q12	-	-

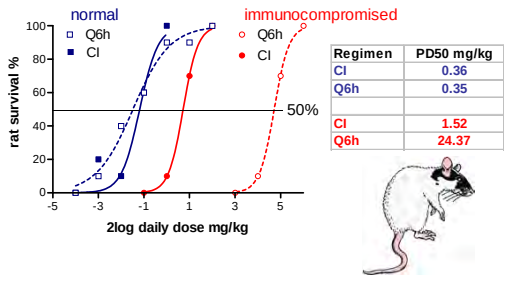
MIC = 1 mg/L

Mouton et al AAC 2007

Pharmacodynamics of beta-lactams

- 40 % *f*T>MIC results in a static effect
- This can be explained by the characteristics of the drug
- For most (non-severe) infections, this is probably enough because of the presence of the immune system

Rat survival : 4 days Continuous Infusion vs Q6h



Regimen	PD50 mg/kg
CI	0.36
Q6h	0.35
CI	1.52
Q6h	24.37

Adapted from Roosendaal AAC 1986

Continuous Infusion
The ADDITIONAL EFFECT

- Theoretically , >4 x MIC would be optimal
  - More killing – absence of immune system
  - *EARLIER EFFECT - not measured in models*
  - *Is 24 h an adequate time to measure effect?*

Why do clinical studies show no benefit?

Clinical Studies comparing CI an II

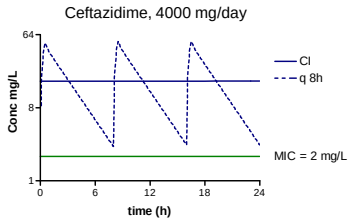
- No good clinical randomized prospective trial showing superiority of CI
- Because of:
  - Do we actually *need* a maximum effect?
  - Lack of power (N)
  - Lack of difference in T>MIC
  - Other factors we do not know about
    - Physiological effects
    - Resistance

CI vs II: lack of power (1)

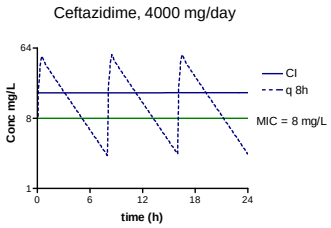
- Most studies are designed to study pharmacokinetics in relatively small groups
- Heterogeneous groups of patients
- Inclusion/exclusion : causing MO, second drug
- Most studies *infer* superiority of CI from a PK analysis but do not actually show superiority

CI vs II: lack of power (2)

CI vs II : how to demonstrate no difference



CI vs II : how to perhaps show differences



So what are the arguments
to use continuous infusion clinically?

Pd arguments:
- Low maximum kill rate, small difference min and max kill

Animal studies showing CI > II
IVPM studies showing CI > II
Anecdotal reports
Cheaper!!
Immunocompromised patients?
ICU?
Hometherapy?
But….. Resistance issues not resolved

- Relapsing UTI elsewhere,
- Self-catheterisation
- Ill, 40 °C, chills , RR 80/50
- L/ CRP 310, WBC 22, Creat 150 μmol/l (weight ~60 kg), urinalysis: leucocytes +++
- D:/ urosepsis
- R:/cefriaxone 1 dd 2 g + gentamicin 1 dd 320 mg iv

- Do you agree with the antibiotic policy ?

Do you agree with the antibiotic policy ?

- A. Yes, I need to cover all eventualities
- B. Yes, a serious disease needs combination therapy for synergy and both drugs are broad Spectrum to assure that
- C. A and B

- Relapsing UTI elsewhere,
- Self-catheterisation
- Ill, 40 °C, chills , RR 80/50
- L/ CRP 310, WBC 22, Creat 150 μmol/l (weight ~60 kg), urinalysis: leucocytes +++
- D:/ urosepsis
- R:/cefriaxone 1 dd 2 g + gentamicin 1 dd 320 g iv

- BC en UC: *Pseudomonas aeruginosa*
- How do you adjust the antibiotic regimen ?

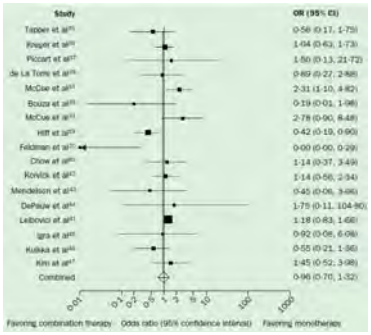
How do you adjust?

- A. piperacillin + tobramycin
- B. piperacillin + ciprofloxacin
- C. ciprofloxacin monotherapy
- D. piperacillin monotherapy

There is clinical trial evidence for combination therapy for in:

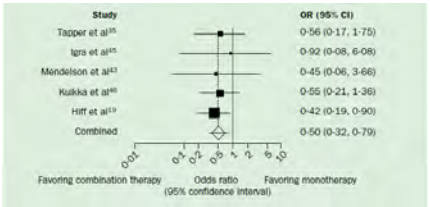
- A. Septic shock
- B. Pseudomonas pneumonia
- C. Neutropenia
- D. There is no evidence

> 6 meta analyses of clinical trials
> show no superiority of beta-lactam + aminoglycoside
> to beta-lactam alone for the treatment of
> sepsis, fever eci etc.



Safdar et al., Lancet Infect Dis 2004

Pseudomonas only – reduction in mortality



Safdar et al., Lancet Infect Dis 2004

Paul et al, BMJ 2004 : 64 trials — no difference in outcome; increase in toxicity (aminoglycosides)

Safdar et al, LID 2004 : 17 trials — no difference in outcome except pseudomonas

Why combination therapy ?

- A. to improve the outcome (addition/ synergy)
- B. to treat a (presumed) resistant Pseudomonas
- C. to prevent a resistant Pseudomonas
- D. more than 1 answer is correct

Present problems

Outcomes are different by patient characteristics

Combination studies may not have been powered adequately

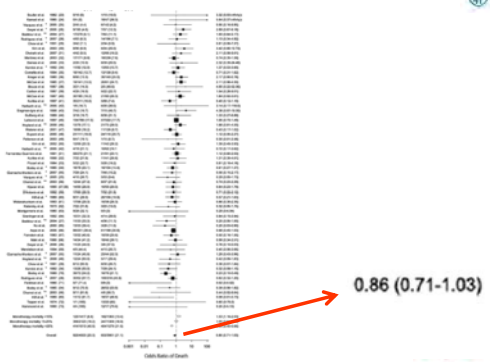
Effect may depend on relative susceptibility (pseudomonas)!

Present problems

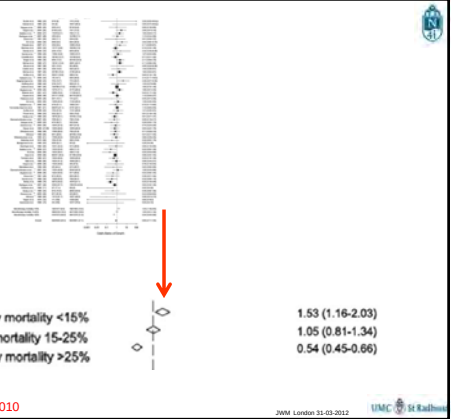
Outcomes are different by patient characteristics

Combination studies may not have been powered adequately

Effect may depend on relative susceptibility (pseudomonas)!



Kumar et al CCM 2010



Kumar et al CCM 2010

Is there circumstantial evidence?

TABLE 1. Bactericidal activity of tobramycin and ceftazidime given alone or in combination towards a tobramycin and ceftazidime resistant *P. aeruginosa*, expressed as the $AUKC_{0\text{-}24h}$ (± SD) determined in conventional time-kill experiments

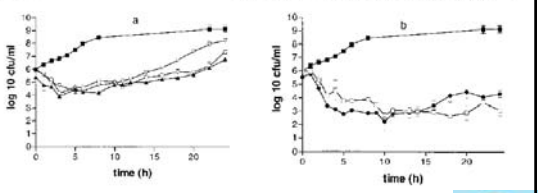
Antibiotic concentration	$AUKC_{0\text{-}24h}$			*P* value[a]
	Tobramycin monotherapy	Ceftazidime monotherapy	Combination therapy	
2 × MIC	93 ± 5	102 ± 2	77 ± 7	0.131
1 × MIC	126 ± 4	122 ± 3	89 ± 3	0.008
1/2 × MIC	148 ± 1	141 ± 1	95 ± 1	0.001
1/4 × MIC	159 ± 5	149 ± 4	123 ± 1	0.012
1/8 × MIC	173 ± 4	156 ± 1	140 ± 1	0.001

[a] *P* value obtained by comparing the best single agent exposure to the combination agent exposure.

den Hollander JG ea,
Antimicrob Agents Chemother.
1997 Jan;41(1):95-100

single tobra/cefta

combination



den Hollander JG ea,
Antimicrob Agents Chemother.
1997 Jan;41(1):95-100

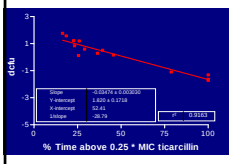
Pk/pd index effect relationships for single drug in mouse thigh model, time > 0.25 for beta-lactam, AUC for aminoglycoside and quinolone

Predict the effect of the combination based on these relationships for varying dosing regimens

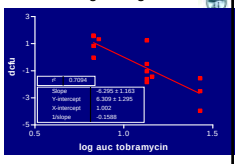
Correlate predicted with actually measured effects of the combinations

Mouton ea., aac 1999

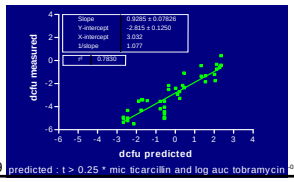
Single drug



Single drug



Predict effect combination



Mouton ea., aac 1999 predicted : t > 0.25 * mic ticarcillin and log auc tobramycin

- Antibiotic therapy for Pseudomonas aeruginosa bacteremia: outcome correlations in a prospective study of 200 patients.
- Mortality :
  monotherapy 47%
  combination therapy 27%

Hilf M ea, Am J Med. 1989 Nov 87(5):540-6

Combination therapy is useful when a checkerboard shows synergy ans is one of the reasons trials have shown no benefit

- A. Yes
- B. No
- C. Only in certain conditions

22nd European Congress of Clinical Microbiology and Infectious Diseases 2012, London

Impact of resistance on treatment and dosing decisions

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

Clinical Case

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

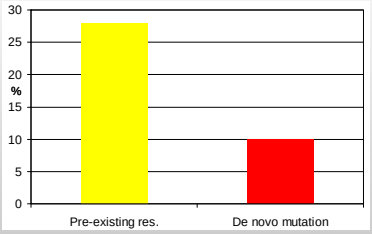
Day 1	Surgical prophylaxis: cefazolin 1g			
	Postoperative fever: levofloxacin 250 mg q12 h			
Day 7		K1 U	ESBL-producing K. pneum.: res. cipro, genta	SHV-12, TEM-1
	imipenem-containing regimen (250 mg/6 h during) for 2 weeks			
Day 11		K2 U	Imipenem MIC↑	MBL (VIM-1)
Day 14		K3 U	As K2	
Day 25		K4 U	Resistant to all ß-lactams (fully resistant to imi)	
	tigecycline (100 mg/ 50 mg/12 h for 1 week)			
Day 32		K5 B	Res tigecycline	
Day 36		K6 B	As K5	
	Ertapenem 1 g/24 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

Acquisition / Emergence of Resistance

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

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



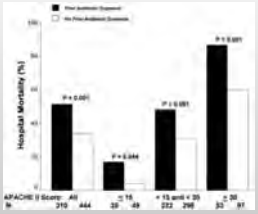
BC van Hees et al: JAC, 2011 66 (8): 1739-1744

Prior Antibiotic Exposure

Table 2. Patients infected with Gram-negative organism(s) susceptible to commonly prescribed antimicrobials for Gram-negative infections [a]

Antimicrobial Agent	Prior Antibiotic Exposure (n = 310)	No Prior Antibiotic Exposure (n = 444)	p
Cefepime	71.0%	93.0%	< .001
Pperacillin–tazobactam	68.1%	88.5%	< .001
Imipenem/meropenem	80.0%	97.5%	< .001
Ciprofloxacin	60.3%	82.4%	< .001
Gentamicin	73.9%	92.1%	< .001
Multidrug-resistant [b]	37.4%	11.3%	< .001

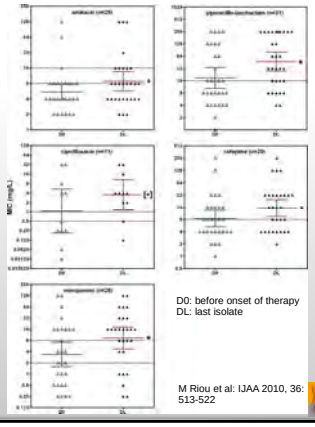
[a] Patients with polymicrobial bacteremia had to have all isolated bacteria susceptible to the antibiotic



M. Johnson et al: Crit Care Med. 2011;39:1859-1865

Emergence of resistance

Pseudomonas HAP/VAP inf
Standard dosages in ICU

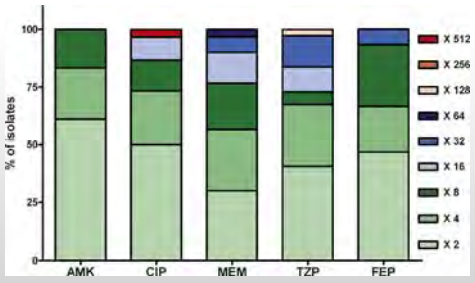


D0: before onset of therapy
DL: last isolate

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

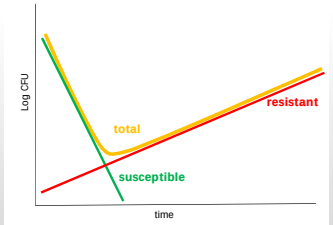
Emergence of Resistance

Pseudomonas HAP/VAP infections
Standard dosages in ICU



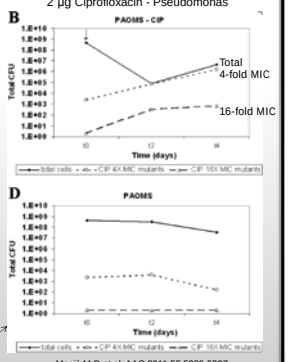
M Riou et al: IJAA 2010, 36: 513-522

Bacterial Population Analysis



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

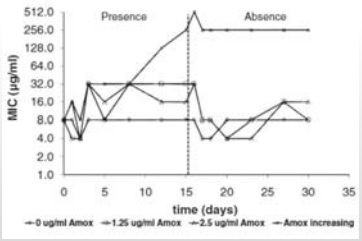
2 µg Ciprofloxacin - Pseudomonas



Control

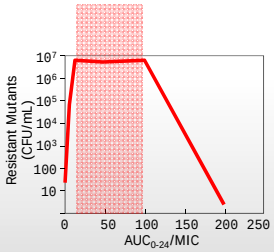
Macià M D et al. AAC 2011;55:5230-5237

De Novo acquisition of resistance by E. coli



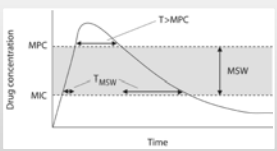
M van Horst et al: Microb Drug Res 2011; 17 (2)

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

PK/PD - Quinolones

12 patients with VAP (500 mg daily levofloxacin)

Pharmacokinetic parameters

$fC_{max,ss}$ (mg/L)	8.13±1.64
$fC_{min,ss}$ (mg/L)	0.52±0.32
V_d (L)	84.49±19.54
V_d (L/kg)	1.18±0.24
$T_{1/2\beta}$ (h)	6.23±1.60
CL (mL/min)	178.09±57.98
CL (mL/min/kg)	2.54±0.95
fAUC (mgh/L)	49.63±15.60

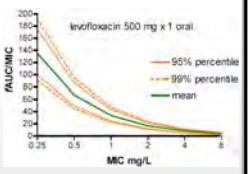
$fAUC_{0-24}$/MIC 70-90, for maximal effect >250

R. Benko et al: IJAA 2007; 30:162-168

PK/PD - Quinolones

12 patients with VAP (500 mg daily levofloxacin)

Target PK/PD parameters	Study MIC	Dedicated MIC values			
	0.31mg/L	0.25mg/L	0.5mg/L	1mg/L	2mg/L
C_{max}/MIC					
10	12	12	12	8	0
12	12	12	12	5	0
AUC/MIC					
30	12	12	12	12	7
50	12	12	12	11	1
100	12	12	11	1	0
125	12	12	7	0	0
250	4	7	0	0	0



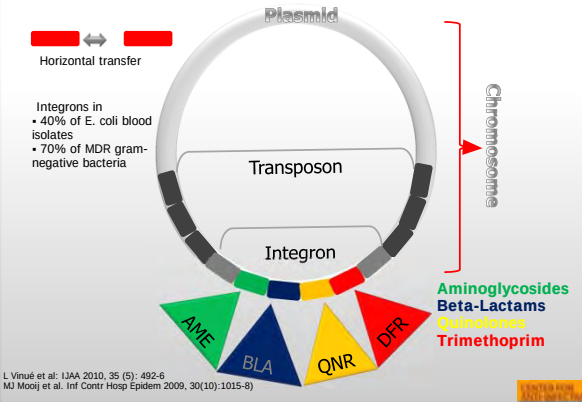
EUCAST technical document 2007

EUCAST breakpoint: ≤1mg/L

Protein binding ~30%

R. Benko et al: IJAA 2007; 30:162-168

Coselection: Mobile Genetic Elements

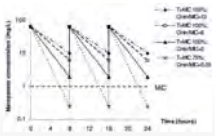


L Vinué et al: IJAA 2010, 35 (5): 492-6
MJ Mooij et al. Inf Contr Hosp Epidem 2009, 30(10):1015-8)

Drug Exposure - Selection of Resistance

Meropenem - Pseudomonas

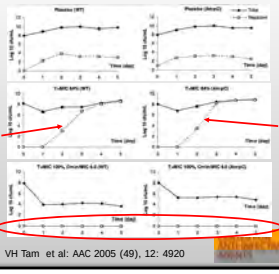
- P. aeruginosa: wild type + AmpC stably derepressed mutant (MIC = 1 mg/l)
- High inoculum, neutropenic



No selective pressure with placebo

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

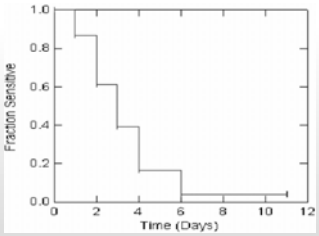
Optimized meropenem exposure
T>MIC=100%, C_{min}/MIC=6:
no growth



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

Resistance Development - Carbapenems

Pseudomonas: Time to initial emergence of resistance
(Pseudomonas wildtype MIC 1mg/L)

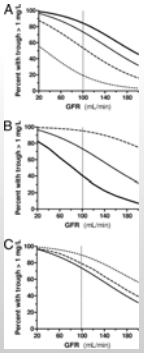


PK/PD_{res}: t>6xMIC
Doripenem 1g q8h (inf 4h): 50% t>6x MIC

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

PK/PD - Carbapenems

Percentage of simulated patients with different GFR levels in whom imipenem plasma concentrations covered the MIC_{90} of the most frequent pathogens (1 mg/L) over the whole dosing interval



Infusion time 30 min:

1000 mg q 6h
750 mg q 6h
500 mg q 6h
250 mg q 6h

Infusion time 30 min:

500 mg q 4h
750 mg q 6h
1000 mg q 8h

750 mg q 6h:

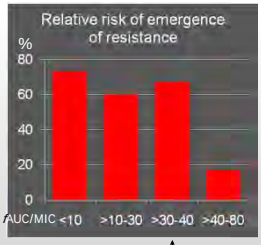
Inf. 120 min
Inf. 60 min
Inf. 30 min

EUCAST breakpoint:
Enterobact. ≤2mg/L (500mgx4)
Pseud: ≤4mg/L (1gx4)

Lamoth F et al. AAC 2009;53:785-787

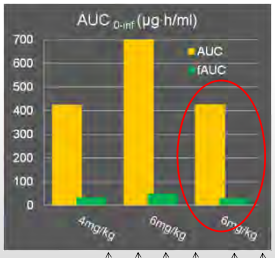
Drug Exposure - Selection of Resistance

Daptomycin
PK/PD for resistance suppresssion:
*f*AUC/MIC>40



KE Bowker et al: ICAAC 2009

EUCAST/CLSI breakpoint for staphylococci ≤1mg/L based on 4mg/kg dosing



Volunteers
Neutropenic patients with fever
*f*AUC ~ 13-55

BH Dvorchik et: al AAC 2003, 47:1318-23
JS Bubalo et al: AAC 2009, 53:428-34

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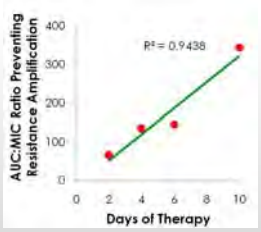
Resistance Development – Treatment Duration

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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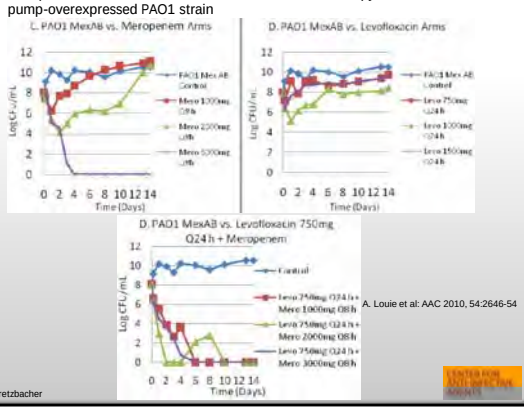
Resistance Development - Combination

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 – antibiotics impact colonising bacteria
- Antibiotic dosage regimens influence probability of resistance emergence

- Optimize dosing if MIC unknown or expected to be elevated
- Monitor PK in high risk patients
- Reevaluate duration of therapy frequently
- Consider drug combinations

Dose Adjustments in Special Patient Populations

Prof. Hartmut Derendorf
University of Florida

Special Populations

- Age
- Body Weight
- Renal Impairment
- Hepatic Impairment
- Disease

Reasons for biological variability in pharmacokinetic parameters

Changes in

- intrinsic clearance
  - e.g. enzyme and transporter activity
- drug binding
  - e.g. plasma protein binding, tissue binding
- blood flow
  - e.g liver blood flow, renal plasma flow
- fluid volumes
  - e.g. total body water, extracellular water
- bioavailability
  - e.g. rate and extent of absorption

Neonates

- low renal clearance
- low metabolic clearance
- relatively more body water
- decreased protein binding
- longer half lives
- rapid changes

Body Water

Age	TBW [%]	ECF [%]	ICF [%]
Fetus (<3 months)	90	65	25
Neonate (premature)	85	50	35
Neonate (term)	75	40	35
Infant (4-6 months)	60	23	37
Adolescent	60	20	40
Adult	60	20	40

Body Water

Volume of distribution

Aminoglycosides

adults	0.2-0.3 L/kg
infants and children	0.5-1.2 L/kg

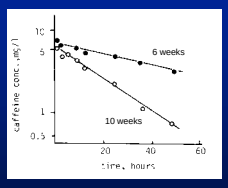
⇨ higher loading dose
⇨ longer dosing interval

Metabolism

Maturation of metabolic pathways

birth	sulfatation
1st week	reduction, oxidation
1 month	acetylation
2 months	glucuronidation
3 months	glycine conjugation
	glutathione conjugation
	cysteine conjugation

Metabolism



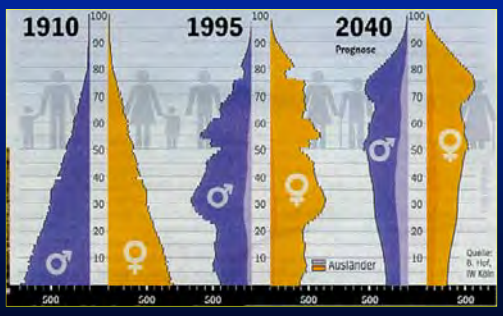
Caffeine levels in the same baby at 6 and 10 weeks of age.

The half life decreased from 41 hours to 16 hours (Aranda et al., 1979).

Renal Function

Age	GFR [ml/min]	RPF [ml/min]
1-10 days	15-45	20-125
1 month	30-60	100-400
6 months	50-100	400-500
1 year	80-120	500-600
1-70 years	80-140	500-700
70-80 years	70-110	250-450
80-90 years	45-85	200-400

Demographics



Polypharmacy in Elderly

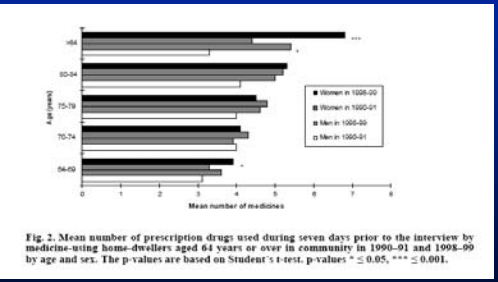
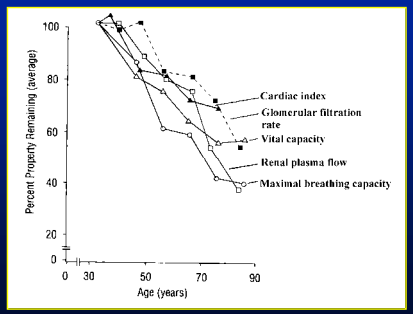


Fig. 2. Mean number of prescription drugs used during seven days prior to the interview by medicine-using home-dwellers aged 64 years or over in community in 1990–91 and 1998–99 by age and sex. The p-values are based on Student's t-test. p-values * ≤ 0.05, *** ≤ 0.001.

T.Linjakumpu, 2003

Physiological Functions and Age



Rowland & Tozer, 1995

Body Weight

- 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

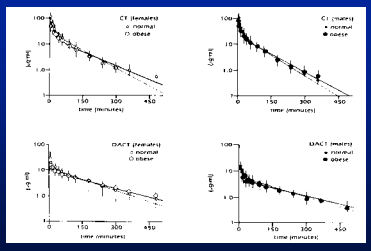
Hydrophilic Drugs:

Little change in Vd, decrease in Vd/kg

Lipophilic Drugs:

Increase in Vd, increase in Vd/kg

Body Weight



Cefotaxime plasma levels after i.v.-bolus (1 g) to normal (90-110 % of IBW) and obese (190-210 % of IBW) subjects

Yost & Derendorf, Ther. Drug Monitor. 8, 189-194 (1986).

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

Adjusted Body Weight (Dosing Weight)

Aminoglycosides

ABW = IBW + 0.4·(TBW-IBW)

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

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

Chronic Kidney Disease

- Major world-wide health concern
- In US number of patients requiring dialysis or transplant is projected to increase from 340,000 in 1999 to 651,000 in 2010
- National Kidney Foundation-attempts to standardize definition, stages and laboratory tests to assess kidney function

Am J Kidney Dis. (2000) 366 suppl 2:S1–S279
S-M Huang *et al.* Clinical Pharmacology & Therapeutics (2009) 86 5, 475–479

Renal Dysfunction and PK

- **Absorption**
  - increased t_{max} for certain drugs in severe renal dysfunction
  - Changes pre-systemic elimination
- **Distribution**
  - Plasma protein binding of many acidic drugs decrease in renal impairment
  - α_1-Acid glycoprotein levels may show an increase
  - Changes in volume of distribution
- **Metabolism**
  - Renal dysfunction may alter even non-renal elimination
  - Accumulation of active metabolites
- **Elimination**
  - Transporters
  - Renal failure may affect multiple organ systems

Dose adjustments!

Cockcroft-Gault Equation

- Derived from 249 men aged 18-92, with and without CKD
- No women were included!
- Factor for females is hypothetical
- Estimates are not adjusted for BSA
- Available modifications-use of ideal/adjusted body weight

$$\text{CrCl (ml/min)} = \frac{[140 - \text{age(years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \times (0.85 \text{ for females})$$

- **Most widely used**
- **Used by FDA for labeling decisions**

Estimated GFR (eGFR) from MDRD Study

- Modification of Diet in Renal Disease (MDRD) Study
- Derived from 1628 men and women with CKD
- GFR adjusted to BSA-accounts for different body sizes
- Standardized serum creatinine values

$$eGFR\ (ml/\min/1.73m^2) = 175 \cdot SCr_{std}^{-1.154} \cdot age^{-0.203} \cdot 0.742\,(female) \cdot 1.212\,(African - American)$$

- **Several versions available**

SCr_{std}: serum creatinine from a standardized assay

National Kidney Foundation Defines Five Stages of CKD

Stage	GFR (ml/min/1.73m²)	Description
1	≥ 90	Normal or ↑GFR
2	60-89	Kidney damage, Mild ↓GFR
3	30-59	Moderate ↓GFR
4	15-29	Severe ↓GFR
5	<15 (Dialysis)	Kidney failure

Renal Diseases

- degree of renal failure can be quantified by the creatinine clearance
- effect of renal failure is most significant if a large fraction of the drug is excreted into the urine

Calculation of dose in renal impairment

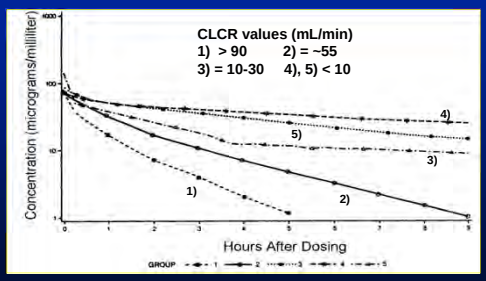
$$D_{pat} = D_{norm} \cdot [\, 1 - f_{ren} \cdot (1 - RF)]$$

D_{pat} Dose for patient with renal impairment
D_{norm} Dose in normal patient
f_{ren} Fraction of drug excreted into urine
RF Renal function (fraction of normal, e.g.CLcreat of 25 ml/min (20 % of normal) means RF = 0.2)

Combinations

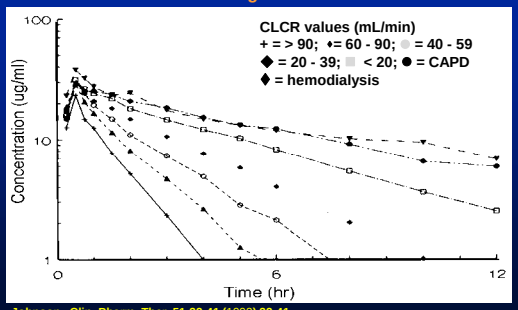
- **Ticarcillin/Clavulanic Acid (Timentin®)**
- **Amoxicillin/Clavulanic Acid (Augmentin®)**
- **Ampicillin/Sulbactam (Unasyn®)**
- **Piperacillin/Tazobactam (Zosyn®)**

Sulbactam pharmacokinetics in renal impairment



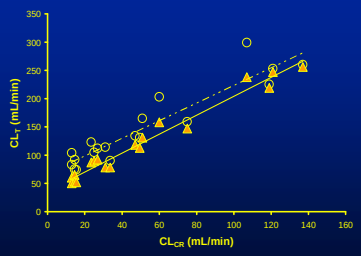
Reitberg, Antimicr. Agents Chemother. 32:503-509 (1988)

Mean TZB plasma concentrations after an IV dose of 3 / 0.375 g of PIP / TZB over 30 min.

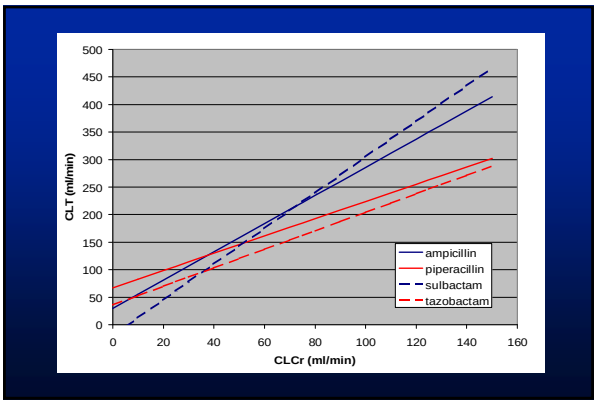


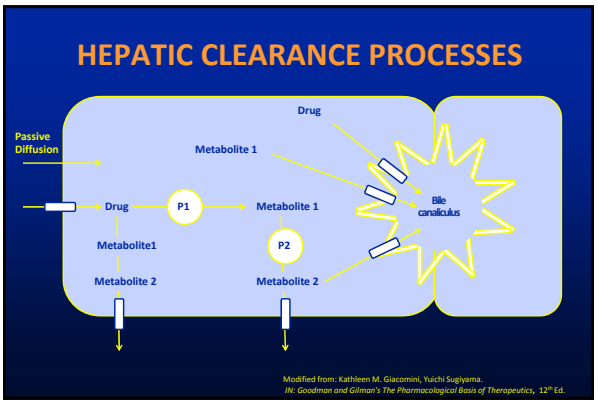
Johnson,. Clin. Pharm. Ther. 51:32-41 (1992) 32-41

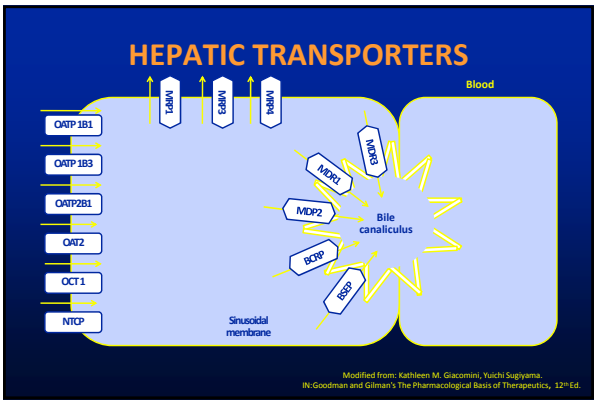
Parallel changes of the PK properties of PIP (○) and TZB (•) during renal impairment (CL_{CR})



Derendorf, Int. J. Clin. Pharm. Ther. 34: 482-488 (1994)


CLT (ml/min)
CLCr (ml/min)
ampicillin
piperacillin
sulbactam
tazobactam


HEPATIC CLEARANCE PROCESSES
Passive Diffusion
Drug
Metabolite 1
P1
P2
Metabolite1
Metabolite 2
Bile canaliculus
Modified from: Kathleen M. Giacomini, Yuichi Sugiyama.
IN: Goodman and Gilman's The Pharmacological Basis of Therapeutics, 12th Ed.


HEPATIC TRANSPORTERS
Blood
MRP1
MRP3
MRP4
OATP 1B1
OATP 1B3
OATP2B1
OAT2
OCT 1
NTCP
MDR3
MDR1
MDP2
BCRP
BSEP
Bile canaliculus
Sinusoidal membrane
Modified from: Kathleen M. Giacomini, Yuichi Sugiyama.
IN:Goodman and Gilman's The Pharmacological Basis of Therapeutics, 12th Ed.

CHILD PUGH SCALE

	1	2	3
Encephalopathy	none	Minimal	Advanced (Coma)
Ascites	Absent	Controlled	Refractory
Bilirubin (µmol/L)	< 34	34 - 51	> 51
Albumin (g/L)	> 35	28 - 35	< 28
Prothrombin Time INR	< 1.7	1.7 – 2.2	> 2.2

- **Interpretation**
  - Child Pugh Score A: 5 – 6 Points
  - Child Pugh Score B: 7 – 9 Points
  - Child Pugh Score C: 10 – 15 Points

Modified from http://www.medscape.com/viewarticle/572659_3, 3.18.2011

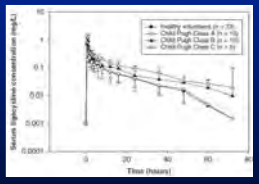
Pharmacokinetics and Safety of a Single Intravenous Dose of the Antibiotic Tigecycline in Patients With Cirrhosis

Joan M. Korth-Bradley, PharmD, PhD, Susan J. Baird-Bellhire, PhD, Alain A. Patat, MD, Steven M. Troy, MS, Gabriele M. Böhauer, MD, Christoph H. Gleiter, MD, Reinhild Buecheler, MD and Marsha Y. Morgan, MB, ChB

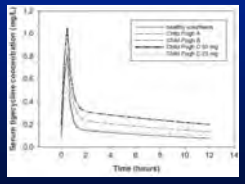
- Single IV Dose 100mg
- Patient Population 25 Participants (21 m/4 f)
- Control Group 23 Participants (19 m/ 4 f)
- Blood and urine samples were collected

PHARMACOKINETIC ANALYSIS

Serum Profiles



Simulated Profiles



Korth-Bradley JM et al. *J Clin Pharmacol* 2011 51: 93 – 101.

PHARMACOKINETIC DATA

Tigecycline	C_{max} (ng/ml)	t ½ (hr)	AUC (ng* h/mL)	CL (L/h)
Healthy	981	18.7	3749	29.8
CPS A	865	19.1	3835	31.2
CPS B	914	23.0	5636	22.1
CPS C	1207	26.8	7656	13.5

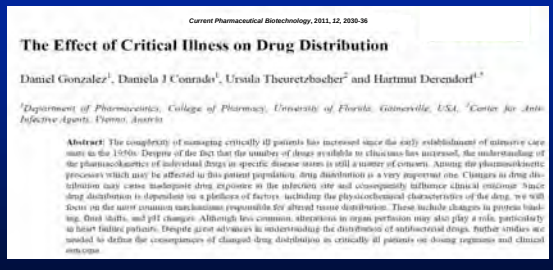
Korth-Bradley JM et al. *J Clin Pharmacol* 2011 51: 93 - 101

SUMMARY

Dosage adjustment recommendations

Drug	Normal Dose	CPS A	CPS B	CPS C
Antimicrobials				
Tigecycline	Loading dose 100mgIV Maintanance dose 50mg q12 IV	-	-	Loading dose 100mgIV Maintenance 25mg q12 hr
Metronidazole	Max. Dose 4g / day IV or PO	Dosage↓ or Interval ↓	Reduced dosage / Interval	50 – 60 % reduced dose/ day
Ceftriaxone	No dosage adjustment without renal impairment needed If renal impairment occurs in addition to liver impairment adult dose should not exceed 2 g/day without close monitoring			
Antimycobacterials				
Rifampin	10mg/kg/day	Dose should not exceed 8mg/kg/day		
Pyrazinamide	2 – 3g/day PO	Contraindicated		

http://www.clinicalpharmacology-ip.com/default.aspx



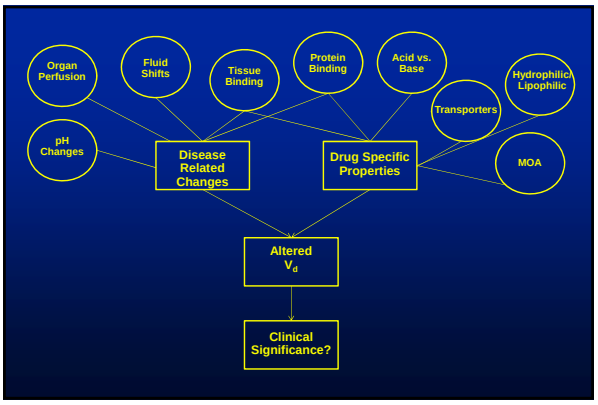
Current Pharmaceutical Biotechnology, 2011, 12, 2030-36

The Effect of Critical Illness on Drug Distribution

Daniel Gonzalez[1], Daniela J Conrado[1], Ursula Theuretzbacher[2] and Hartmut Derendorf[1,*]

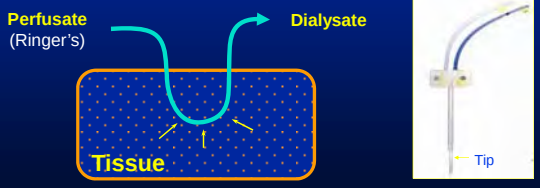
[1]*Department of Pharmaceutics, College of Pharmacy, University of Florida, Gainesville, USA;* [2]*Center for Anti-Infective Agents, Vienna, Austria*

Abstract: The complexity of managing critically ill patients has increased since the early establishment of intensive care units in the 1950s. Despite of the fact that the number of drugs available to clinicians has increased, the understanding of the pharmacokinetics of individual drugs in specific disease states is still a matter of concern. Among the pharmacokinetic processes which may be affected in this patient population, drug distribution is a very important one. Changes in drug distribution may cause inadequate drug exposure at the infection site and consequently influence clinical outcome. Since drug distribution is dependent on a plethora of factors, including the physicochemical characteristics of the drug, we will focus on the most common mechanisms responsible for altered tissue distribution. These include changes in protein binding, fluid shifts, and pH changes. Although less common, alterations in organ perfusion may also play a role, particularly in brain tissue patients. Despite great advances in understanding the distribution of antibacterial drugs, further studies are needed to define the consequences of changed drug distribution in critically ill patients on dosing regimens and clinical outcome.

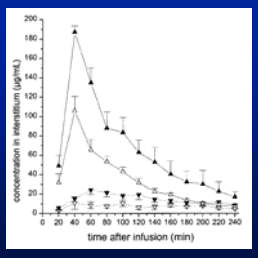


Microdialysis

Microdialysis allows to monitor the free tissue concentrations



Piperacilin in septic shock



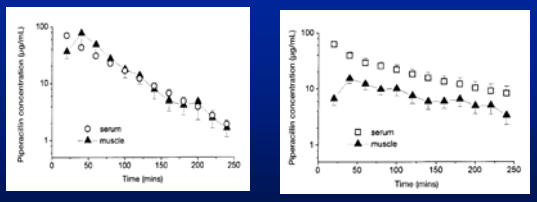
Healthy controls

Septic patients

Piperacilin levels in the interstitial space fluid of skeletal muscle (filled triangles) and subcutaneous adipose tissue (open triangles) of healthy and septic patients after single iv dose of 4mg.

Joukhadar et al, 2001

Piperacillin

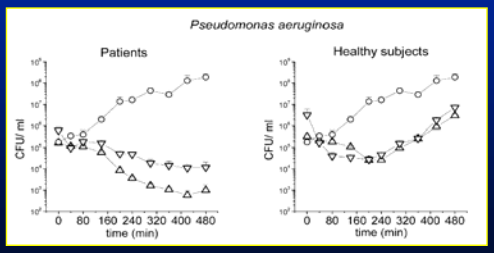


Piperacillin serum and muscle levels in healthy patients and intensive care patients after single iv dose of 4g

Brunner et al, 2000

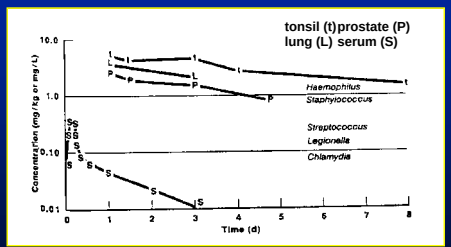
Piperacillin in patients

Piperacillin kill curves (MIC: △ = 2 mg/l and ▽=4 mg/l)



Sauermann et al, 2003

Azithromycin
Tissue Concentrations



500 mg p.o.

from Foulds et al. (1990)

Journal of Antimicrobial Chemotherapy (2008) 61, 235–237
doi:10.1093/jac/dkm476
Advance Access publication 6 December 2007

JAC

Tissue concentrations: do we ever learn?

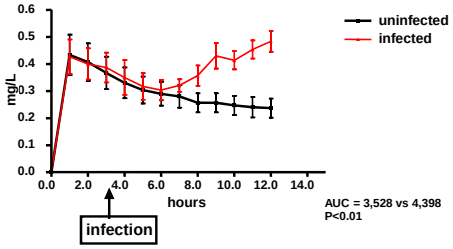
Johan W. Mouton[1]*, Ursula Theuretzbacher[2], William A. Craig[3], Paul M. Tulkens[4], Hartmut Derendorf[5] and Otto Cars[6]

[1]Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Ziekenhuis, Nijmegen, The Netherlands; [2]Center for Anti-Infective Agents, Vienna, Austria; [3]Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; [4]Cellular and Molecular Pharmacology Unit, Université catholique de Louvain, Brussels, Belgium; [5]Department of Pharmaceutics, University of Florida, Gainesville, FL, USA; [6]Department of Medical Sciences, Infectious Diseases, Uppsala University, Uppsala, Sweden

Over the last decades, numerous papers have appeared—and still are appearing—that describe concentrations in tissues in an effort to predict the efficacy of an antimicrobial agent based on these concentrations and MICs for microorganisms. A common method is to use measurements of concentrations in tissue homogenates, comparing these with values derived from the corresponding blood samples and on that basis draw conclusions with respect to the potential clinical use of the drug. This approach is not justifiable for a number of reasons that includes both pharmacokinetic as well as pharmacodynamic causes. This way of presenting data with the derived conclusions is often misleading and may ultimately be harmful in patient care.

Azithromycin

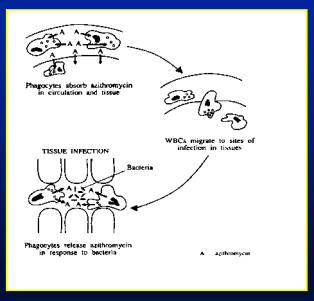
Tissue concentration (IF) of azithromycin (50 mg/kg sc) in infected (S. aureus) and uninfected rat thigh (same animal)



AUC = 3,528 vs 4,398
P<0.01

Scaglione et al., ICAAC 2006

Phagocyte Delivery of Azithromycin



from Schentag et al. (1991)

ISAP

International Society of Anti-Infective Pharmacology

- Workshops at ECCMID and ICAAC
- Symposia at ECCMID and ICAAC
- Joint Symposium with FDA and IDSA
- Website with slides, presentations and tons of information

www.isap.org