Infection Management in the Elderly: Room for Improvement
ESCMID Postgraduate Education Course, 2 - 3 October 2014, Annecy, France

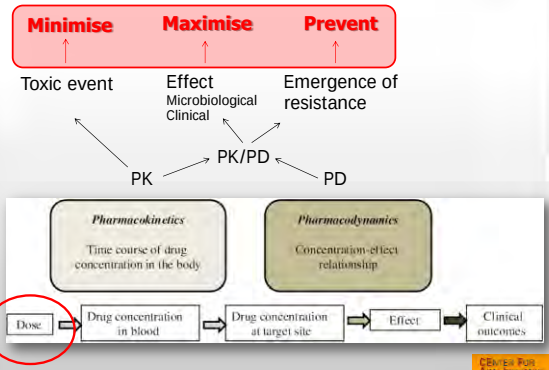
Appropriate antibiotic dosing concepts in elderly with cancer

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

Cancer in the elderly

Age-Specific Incidence Rates, of all cancers excl. non-melanoma, per 100,000 population, UK, 2009-2011

Exposure - Effect - Relationship



Varghese JM et al: Crit Care Clin 27 (2011) 19–34

Pharmacokinetics in elderly with cancer

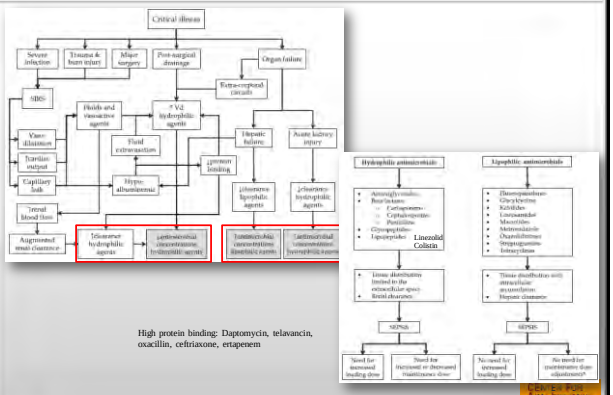
- Disease
  - Very homogenous group
  - PK data not available for elderly with cancer
    - Limited PK data available in critically ill cancer patient groups
    - Published data: Defined critically ill cancer patient groups ~ ICU ~ compassionate-use patient cohorts
- Age related changes

PK – Frail patients

- Reduced clearance
  - About 12 % lower gentamicin clearance
  - Relevant for drugs that undergo significant excretion through glomerular filtration
- Independently associated with increased ICU and 6-month mortalities

C. Johnston et al: Eur J Clin Pharmacol. 2014, 70(5):549-55
D. Le Maguet et al Intensive Care Medicine 2014, 40 (5): 674-682

Physiological changes in critically ill patients



High protein binding: Daptomycin, telavancin, oxacillin, ceftriaxone, ertapenem

S.I Blot et al: Adv. Drug Deliv. Rev. July 2014

Recommended reading

THE LANCET Infectious Diseases

The Lancet Infectious Diseases, Volume 14, Issue 6, Pages 498 - 509, June 2014

Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions

Prof Jason A Roberts PhD a b, Mohd H Abdul-Aziz BPharm b, Prof Jeffrey Lipman MD a b, Prof Johan W Mouton PhD c, Prof Alexander A Vinks PhD d, Dr Timothy W Felton MRCS e, Prof William W Hope PhD f, Dr Andras Farkas PharmD g, Michael N Neely MD h, Dr Jerome J Schentag PharmD i, Prof George Drusano MD j, Dr Otto R Frey PhD k, Dr Ursula Theuretzbacher PhD l, Dr Joseph L Kuti PharmD h, on behalf of The International Society of Anti-Infective Pharmacology and the Pharmacokinetics and Pharmacodynamics Study Group of the European Society of Clinical Microbiology and Infectious Diseases

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The effect of pathophysiology on pharmacokinetics in the critically ill patient — Concepts appraised by the example of antimicrobial agents

Stijn I. Blot a,b,*, Federico Pea b,c, Jeffrey Lipman d,e

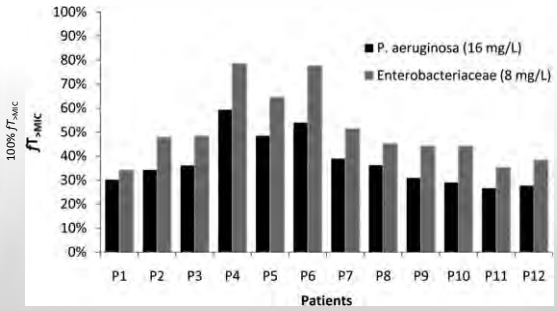
PK of piperacillin/tazobactam in febrile neutropenia

- Cachexia, hypoalbuminemia, development of a third space
- Increase in $t_{1/2}$ and decreased CL
- High variability
  - C_{max} 94.1–1133 mg/L (mean 319.33)
  - C_{min} 0.47–37.65 mg/L (mean 13.50)
  - V_d 0.08–0.65 L/kg (mean, 0.34 L/kg)
  - CL 4.42–27.25 L/h (mean, 9.93 L/h)
  - $t_{1/2}$ 0.55–2.65 h (mean, 1.38 h)
  - AUC 115.12–827.16 mg · h/L
  - Albumin level

IC C Alvarez et al: BMC Pharmacology and Toxicology 2013, 14:59

PK/PD target attainment - 4.5 g piperacillin-tazobactam

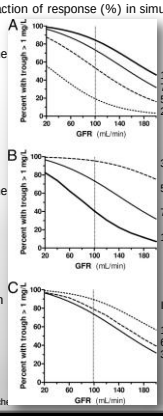
12 febrile neutropenic patients with hematological malignancies, EUCAST MIC breakpoints



Sime F B et al. AAC 2014;58:3533-3537

Probability of Target Attainment with Imipenem

Cumulative fraction of response (%) in simulated febrile neutropenic patients with different GFR levels



Infusion time 30 min

1g q 6h
750mg q 6h
500mg q 6h
250mg q 6h

Infusion time 30 min

3g daily:
500mg q 4h
750mg q 6h
1g q 8h

750mg q 6h

Infusion time:
120 min
60 min
30 min

MIC: 1 mg/L
PK/PD target: 100%t>MIC

Recommended imipenem dosage of 2g/day is insufficient

Optimisation: 500 mg every 4 h or 750 mg in 2-h infusions every 6 h

Lamoth F et al. AAC2009;53:785-787

Dose Optimisation

Monte Carlo Simulation of Doripenem in Febrile Neutropenia

Table 4. Cumulative Fraction of Response (80% $fT_{>MIC}$) Against Various Gram-Negative Pathogens

Organism	Doripenem MIC_{50} (mg/L)[a]	Dose and Infusion Times: 500 mg, 1 hour	500 mg, 4 hours	1000 mg, 1 hour	1000 mg, 4 hours
Escherichia coli	0.06	0.98	0.99	0.99	0.99
Klebsiella pneumoniae	0.12	0.96	0.99	0.95	0.99
Proteus mirabilis	0.50	0.83	0.96	0.92	0.99
Enterobacter cloacae	0.25	0.92	0.99	0.96	0.99
Serratia marcescens	0.25	0.92	0.99	0.96	0.99
Pseudomonas aeruginosa	4.00	0.16	0.28	0.40	0.61

[a]TRUST 13 (2009) surveillance data.[3]

GE Stein et al: Ann Pharmacother 2012;46.

PK/PD – Clinical Outcome

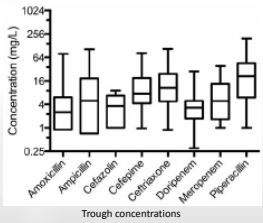
Neutropenic patients with persistent fever attributed to imipenem underdosing

Creatin. clearance (mL/min)	Aetiology of febrile neutropenia	Imipenem dosing schedule	Trough conc.	Duration of fever/clinical course	Modification of dosing schedule	Days to resolution
92	CDI (neutropenic enterocolitis)	0.5 g qid	1 mg/L	3 days/persistent fever and enterocolitis	infusion time 120 min	1
75	FUO	0.5 g qid	<0.25 mg/L	4 days/persistent fever	1 g qid	3
51	FUO	0.5 g tid	0.7 mg/L	6 days/persist. fever	0.5 g qid	1

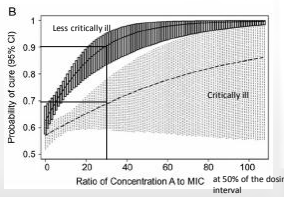
F. Lamoth et al: JAC 2009;64:665-667

PK/PD in critically ill patients

DALI study



Trough concentrations



Dosing and PK/PD Data	Antibiotic (No. of Patients)							
	Amoxicillin (n = 71)	Ampicillin (n = 18)	Cefazolin (n = 14)	Cefepime (n = 14)	Ceftriaxone (n = 33)	Doripenem (n = 13)	Piperacillin (n = 109)	Meropenem (n = 89)
Dosage per 24 H, g	6.0 (3.5–6.0)	12.0 (8.3–12.0)	3.0 (3.0–4.0)	6.0 (5.0–6.0)	2.0 (2.0–4.0)	1.75 (1.50–3.0)	12.0 (12.0–16.0)	3.0 (3.0–4.0)
50% $fT_{>MIC}$ achieved	52.1%	55.6%	100.0%	78.6%	97.0%	100.0%	80.6%	95.0%
50% $fT_{>4xMIC}$ achieved	16.9%	27.8%	50.0%	50.0%	93.9%	69.2%	48.9%	68.8%
100% $fT_{>MIC}$ achieved	18.3%	33.3%	78.6%	78.6%	93.9%	76.9%	67.0%	69.7%
100% $fT_{>4xMIC}$ achieved	11.3%	22.2%	14.3%	71.4%	87.9%	30.8%	30.3%	41.6%

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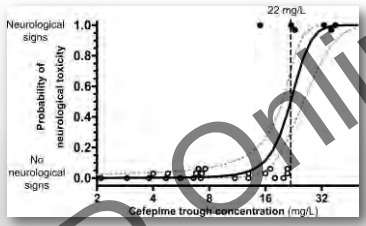
J Roberts et al: CID 2014, 58 (8): 1072

Probability of toxic events

Probability of cefepime-associated neurological toxicity as a function of the cefepime trough plasma concentration in febrile neutropenic patients with mild impairment of renal function



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Lamoth F et al. AAC 2010;54:4360-4367

Vancomycin PK: cancer vs non-cancer

Pharmacokinetics of vancomycin in adult cancer patients

PK parameter	Cancer Group	Non-Cancer Group	P-value
K, hr^{-1}	0.14 ± 0.1	0.14 ± 3.9	0.947
$t_{1/2}$, hr	8.6 ± 7.1	5.4 ± 1.9	0.111
V_d, L	70 ± 45	31.1 ± 8.3	0.002
Cl, ml/min	110.1 ± 42	71.2 ± 22.2	0.005

H. Al-Kofide et al.: J Oncol Pharm Pract 2010;16:245-250

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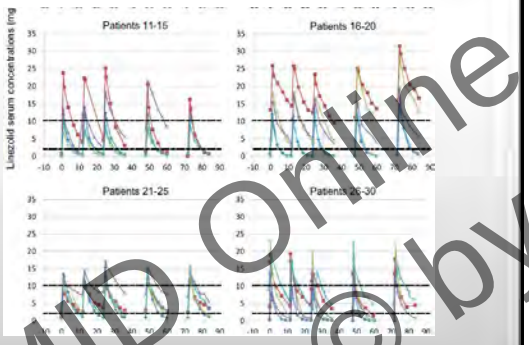
Linezolid

- High variability of linezolid serum concentrations after standard linezolid dosing in critically ill patients.
- Potentially subtherapeutic levels in the majority of patients.
- Potentially toxic levels in a minority of patients.
- Therapeutic drug monitoring!

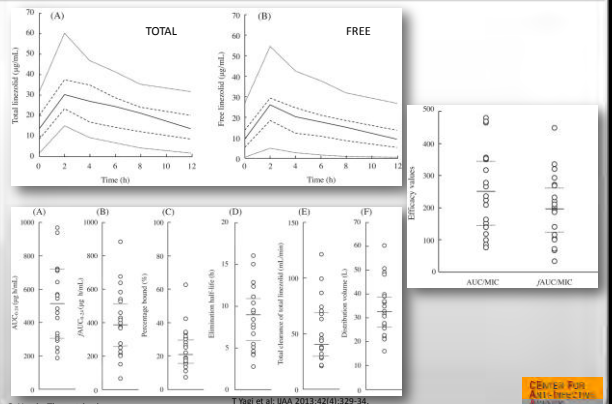
Zoller et al. Critical Care 2014, 18:R148

Linezolid



Zoller et al. Critical Care 2014, 18:R148

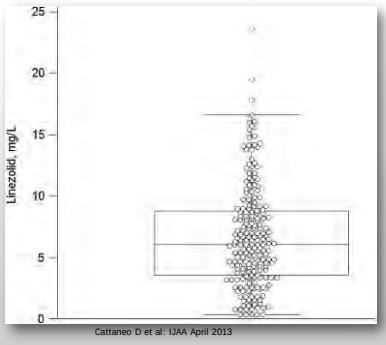
Linezolid in critically ill patients



T Yagi et al: IJAA 2013;42(4):329-34.

PK - Toxicity

Linezolid plasma trough concentrations - haematological toxicity

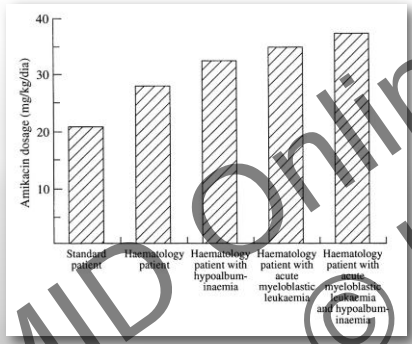


9.3±5.4mg/L vs. 4.4±3.4mg/L; *P*<0.01).

Cattaneo D et al: IJAA April 2013

Dosage optimisation

Initial amikacin dosage recommendations for patients with haematological malignancies



Romano S et al. JAC 1999;44:235-242

PTAs in critically ill / cancer patients

Antibacterial class	PK/PD index predictive for outcome	Required magnitude of the PK/PD index to optimize activity	PTA (%) in severely ill cancer/ICU patients (selected examples)	Dosing strategy
Beta-lactam antibiotics	% *f*t>MIC	% *f*t>MIC: 40-70%, 80-100% in immunocompromised patients	**53%** with imipenem 500mg q4h at MIC 1 mg/L (100 ml/min GFR)	I.v.: Prolonged infusion, continuous infusion; Oral: More frequent dosing per day
Aminoglycosides	AUC_{0-24}/MIC and C_{max}/MIC	AUC_{0-24}/MIC: >150	**55%** with tobramycin 5mg/kg at MIC 1 mg/L	Once daily administration, duration of therapy not longer than 5-7 days, TDM
Glycopeptides: vancomycin	*f*AUC_{0-24}/MIC	AUC_{0-24}/MIC: >400 (total drug, protein binding 50%)	**50%** with vancomycin 2g/day at MIC 2 mg/L (Cl_{ren} 60-120 mL/min)	Dosing according to TDM
Lipopeptides: Daptomycin	*f*AUC_{0-24}/MIC and C_{max}/MIC	AUC_{0-24}/MIC: >800 (total drug, protein binding 90%)	**77%** with daptomycin 6mg/kg/day at MIC 1 mg/L	High once daily dosing, TDM would be beneficial, not enough clinical data
Oxazolidinones: Linezolid	% *f*t>MIC and *f*AUC_{0-24}/MIC	AUC_{0-24}/MIC: >100 and % t>MIC >85% (total drug, protein binding 30%)	**70%** with linezolid 600mg q12 h at MIC 2mg/L	Dosing according to TDM to avoid treatment failure and dose-dependent toxicity
Quinolones	*f*AUC_{0-24}/MIC	*f*AUC_{0-24}/MIC: 70-90 and >250 for maximal effect	**77%** with ciprofloxacin 400mg q8h at MIC 0.25mg/L	High dosages, TDM may be beneficial

U Theuretzbacher: CID 2012 ,54(12):1785-92

Dose Optimisation

- Beta-lactam antibiotics
  - Loading dose, infusion time (2-3 hours), continuous infusion?
  - Short dosing intervall
- Quinolones
  - Increased daily dosage
- Aminoglycosides
  - Increased dosage once daily, TDM, short duration of therapy
- Linezolid
  - Dosing according to TDM (AUC_{0-24}/MIC: >100 and %t>MIC >85%)
- Vancomycin
  - Dosing according to TDM (target trough levels of 15–20 mg/L)

Dosing Strategies

Traditional
One size fits all

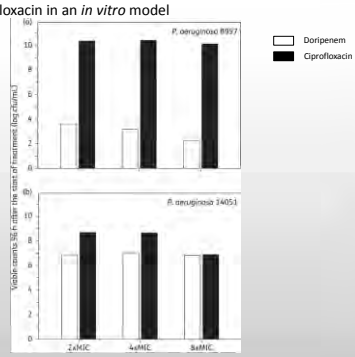
Optimised
Based on population PK
Probability of Target Attainment

Traditional or optimised + TDM
Feedback+dose adjustment during the treatment course

Individualised
From the first dose throughout the therapy
Bayesian Feedback Control integrated in Computerized clinical decision support systems

Concentration–resistance relationship

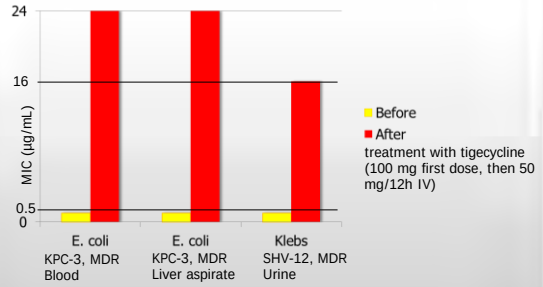
Concentration–resistance relationships with *Pseudomonas aeruginosa* exposed to doripenem and ciprofloxacin in an *in vitro* model



SH Zinner et al. IAC 2013; 68:881-887

Emergence of Tigecycline Resistance

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



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

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

ISAP International Society of Anti-Infective Pharmacology
Founded in 1991
www.isap.org

EPASG ESCMID PK/PD OF ANTI-INFECTIVES STUDY GROUP
European Society of Clinical Microbiology and Infectious Diseases
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