Fokusadaptierte Therapie: Welchen Stellenwert hat die Gewebepenetration?

Universitätsklinikum Essen

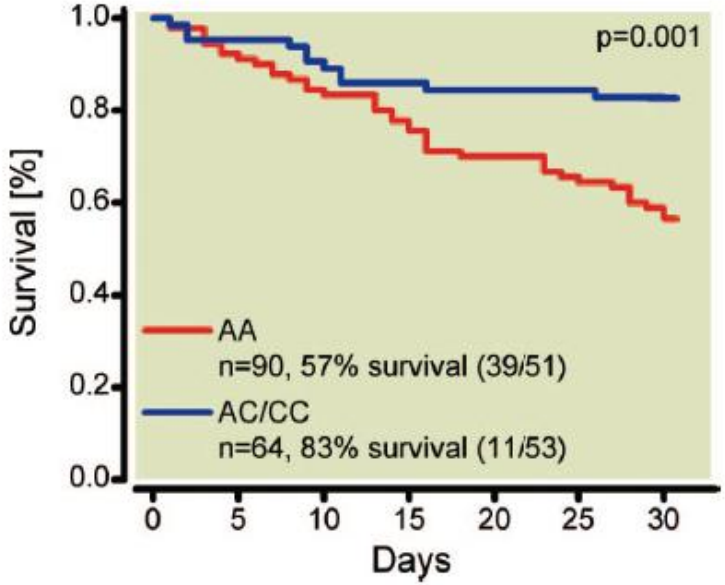
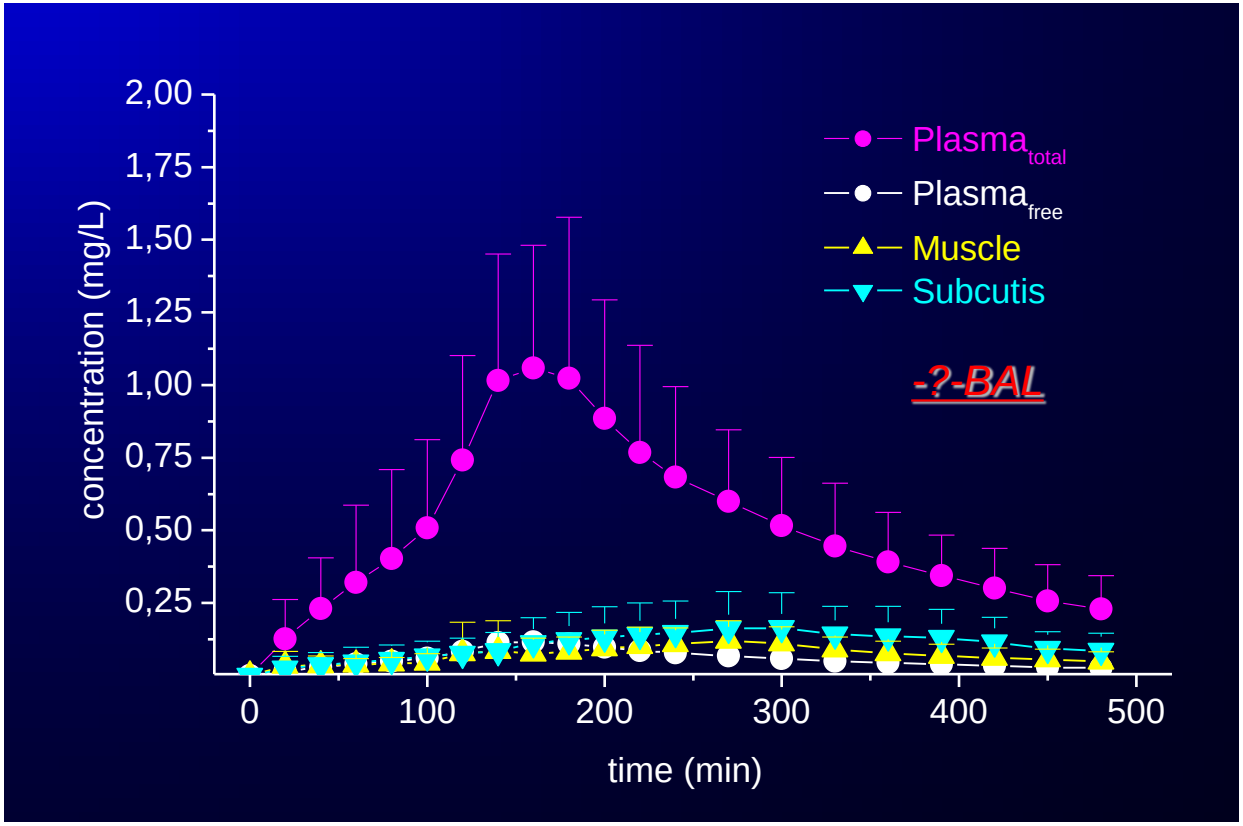


Fig. 1. Thirty-day survival in patients with severe sepsis. Kaplan–Meier estimates were used to calculate probabilities of 30-day survival based on aquaporin (AQP) 5 promoter −1364A/C polymorphism. Thirty-day survival was significantly decreased in AA genotypes compared with carriers of the C-allele.

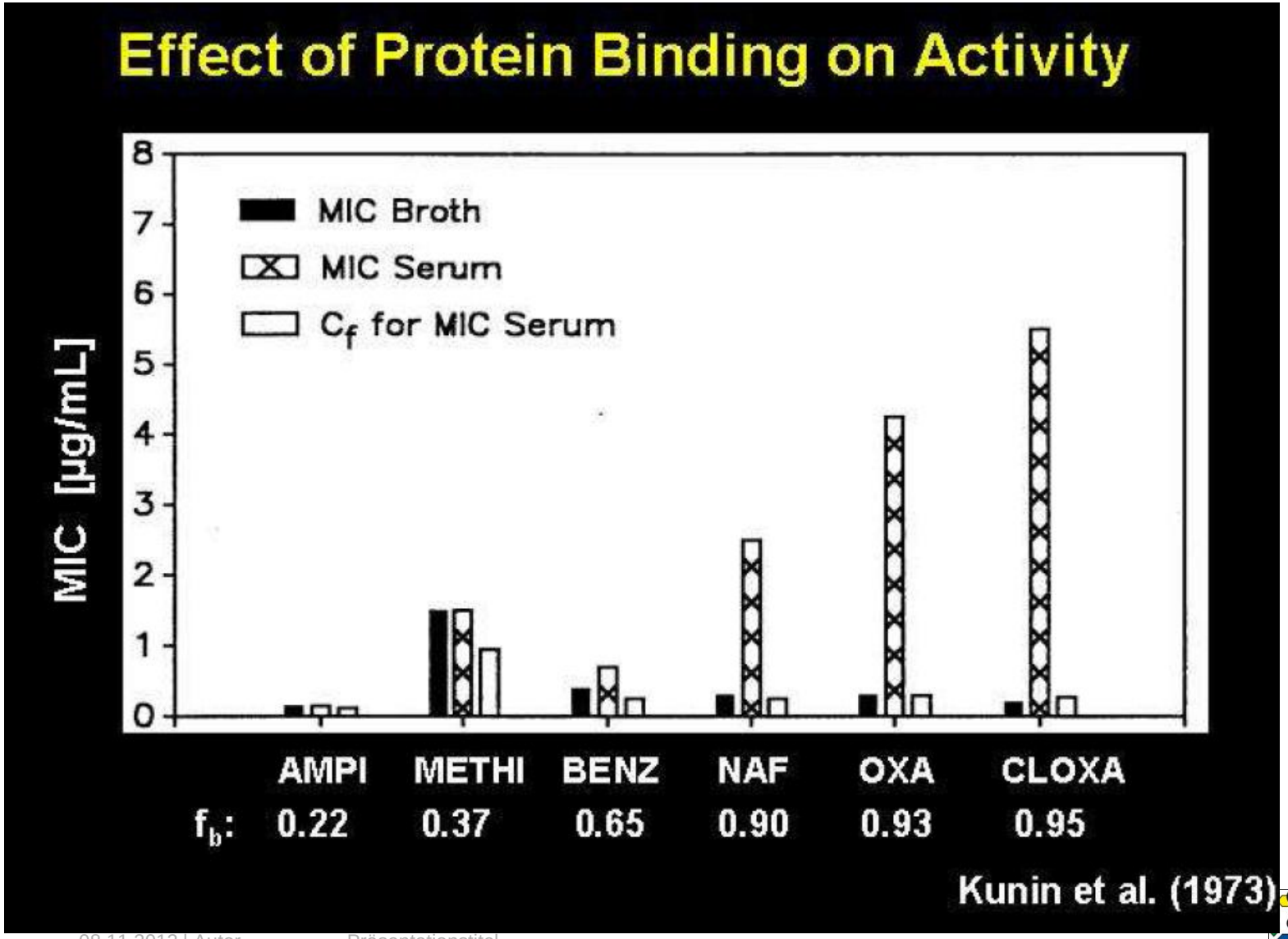
Anesthesiology 2011; 114:912-7 Adamzik *et al.*

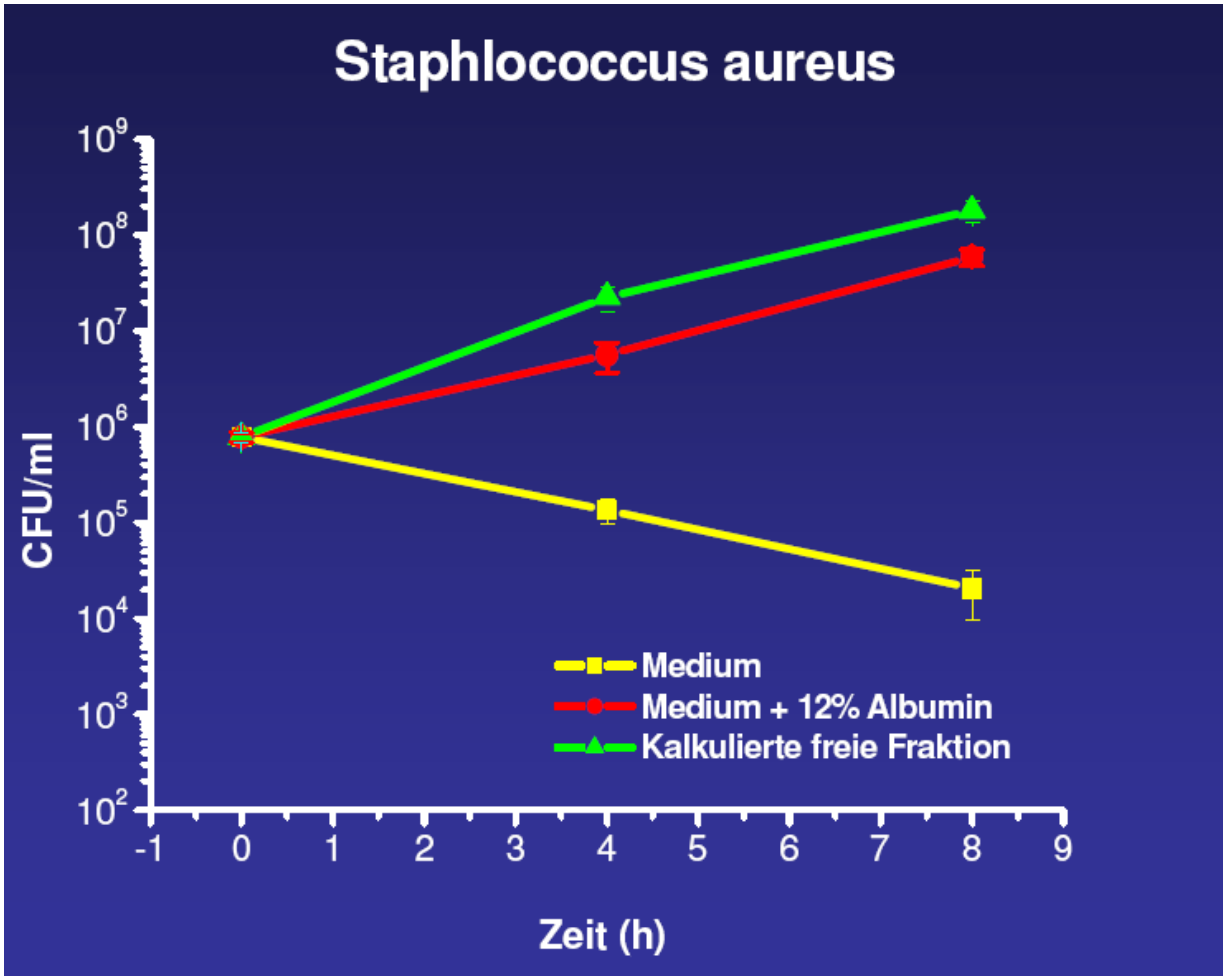
ß-Laktam



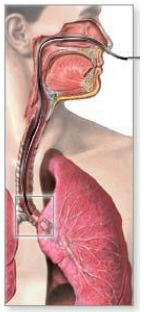
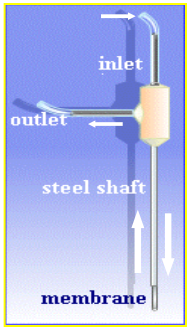
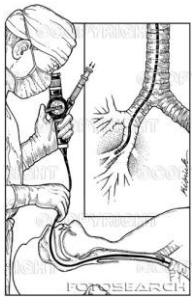
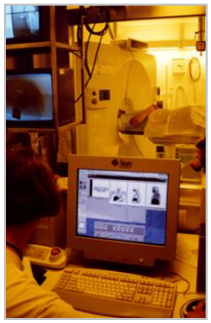
Gattringer. Antimicrob Agents Chemother. 2004

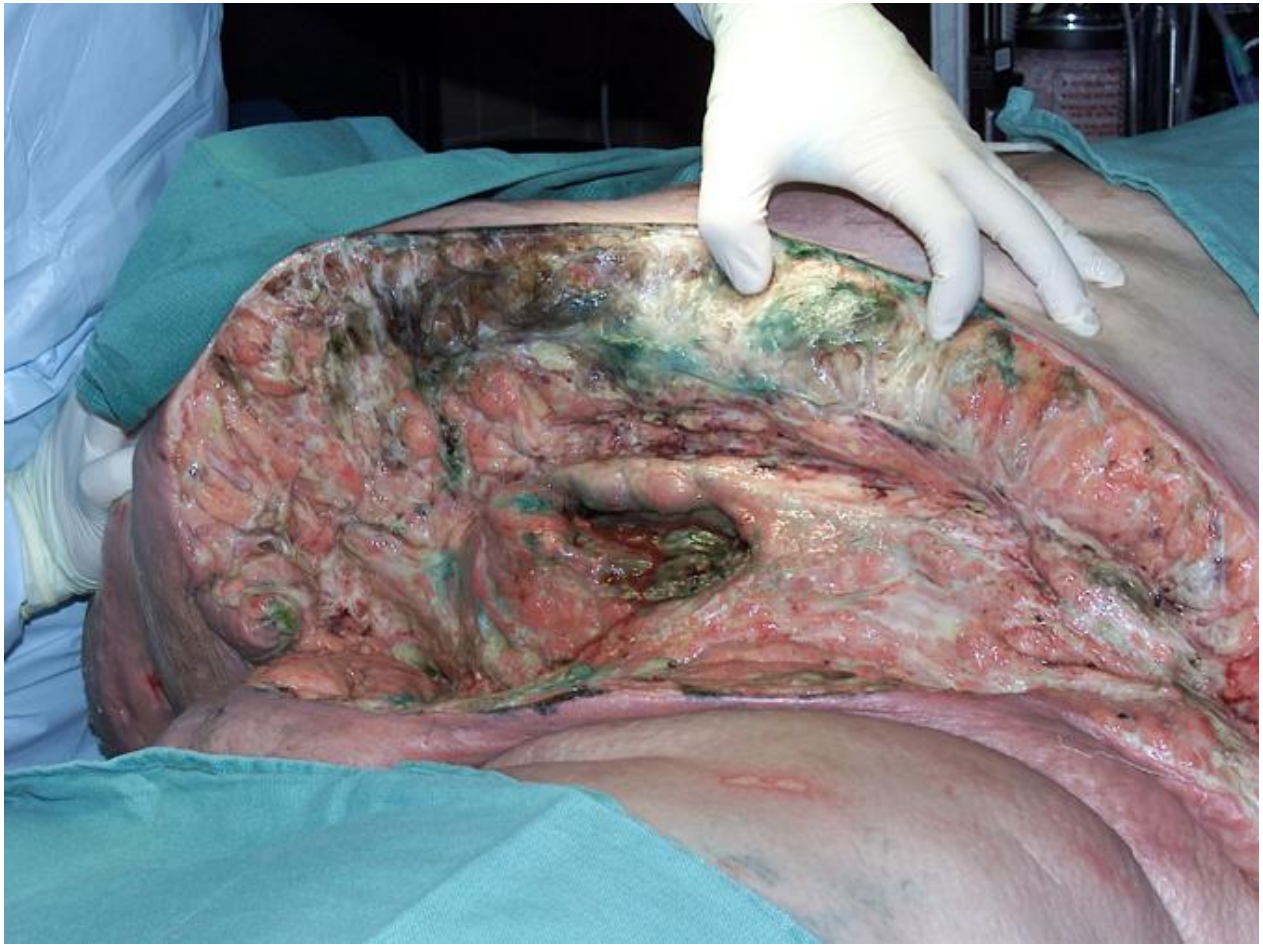
Effect of Protein Binding on Activity





Zeitlinger. J Antimicrob Chemother. 2005

	Biopsie	MD	BAL	HPLC
				
invasiv	+	+	+/-	-
freie Konz	-	+	+/-	+
longitudinal	-	+	-	+
Verfügbar/ Preis	+	-	+	-



Capillary leak syndrome

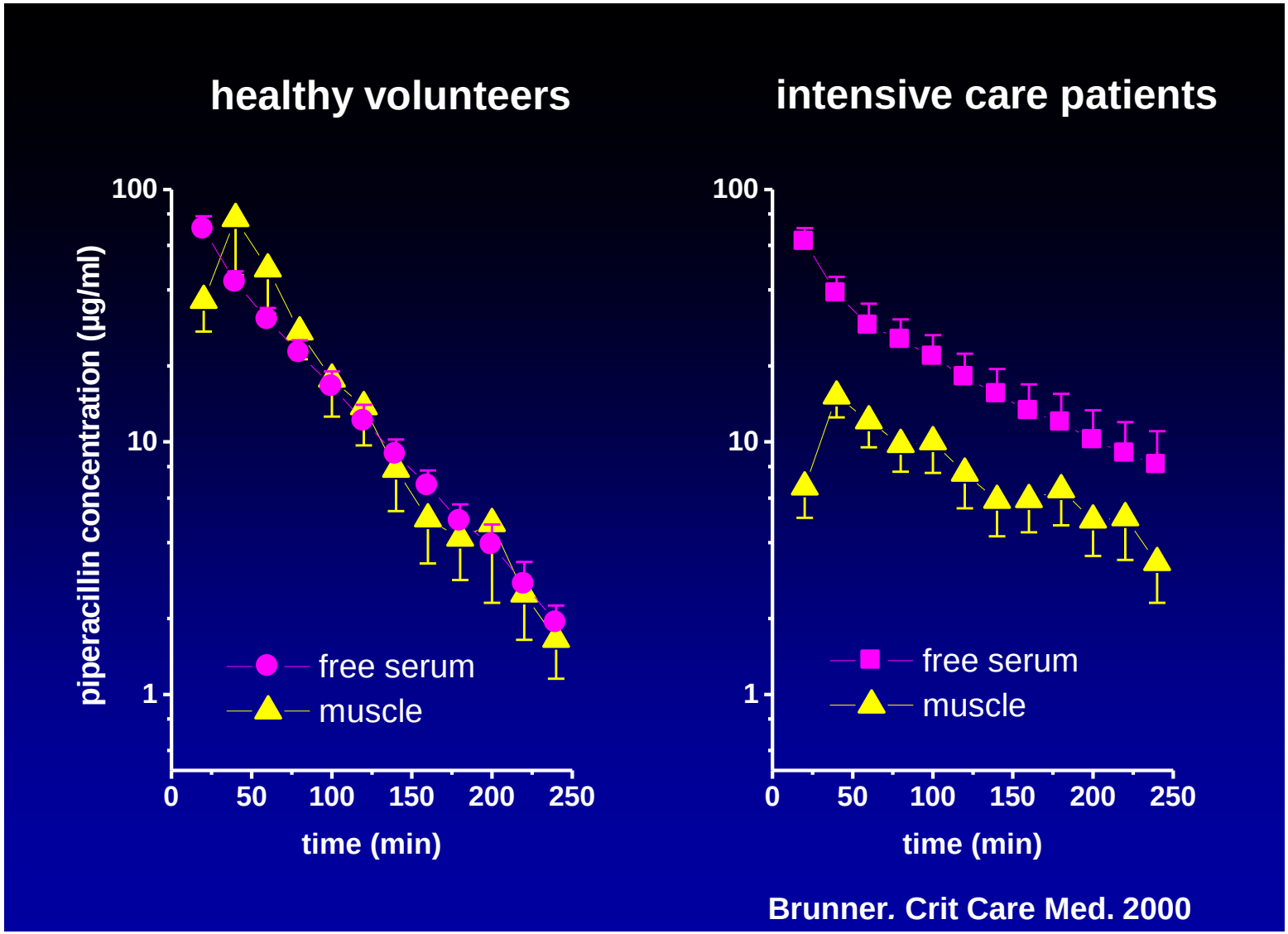
Hypoproteinämie

Anaerober Stoffwechsel

Makro-Mirkozirkulationsstörungen

Medikamenteninteraktionen

Piperacillin



AUC $_{0\text{-}8\text{-}Muskel}$/AUC $_{0\text{-}8\text{-}freie\ Konz\ im\ Plasma}$

Quotient lag zwischen 0.1-0.7 mit einer sehr großen interindividuellen Varianz

Joukhadar, C., M. Frossard, B. X. Mayer, M. Brunner, N. Klein, P. Siostrzonek,H. G. Eichler, and M. Muller. 2001. Impaired target site penetrationof beta-lactams may account for therapeutic failure in patients with septic shock. Crit. Care Med. **29:**385–391.

Frossard, M., C. Joukhadar, B. M. Erovic, P. Dittrich, P. E. Mrass, M. Van Houte, H. Burgmann, A. Georgopoulos, and M. Muller. 2000. Distribution and antimicrobial activity of fosfomycin in the interstitial fluid of human soft tissues. Antimicrob. Agents Chemother. **44:**2728–2732.

Joukhadar, C., N. Klein, B. X. Mayer, N. Kreischitz, G. Delle-Karth, P. Palkovits, G. Heinz, and M. Muller. 2002. Plasma and tissue pharmacokinetics of cefpirome in patients with sepsis. Crit. Care Med. **30:**1478–1482.

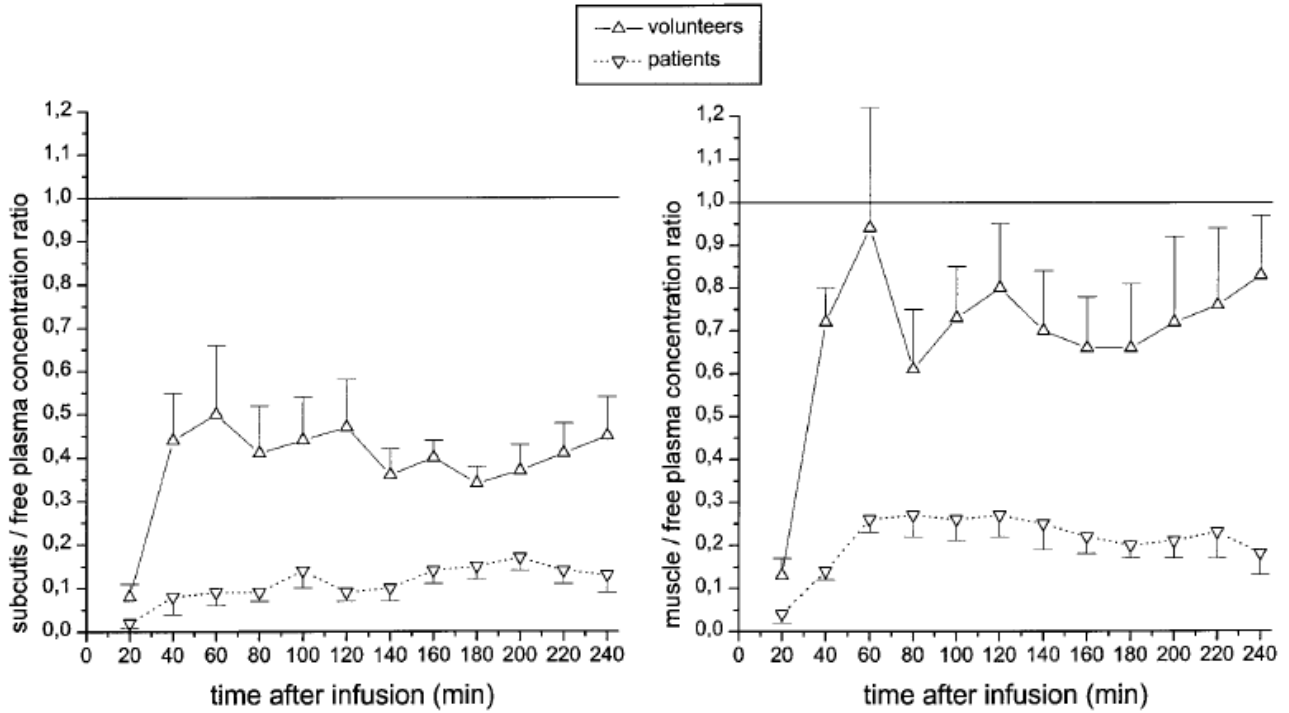


Figure 2. Time course of interstitial space fluid/free plasma concentration ratios, as a measure of piperacillin penetration into subcutaneous adipose tissue (*left panel*) and skeletal muscle (*right panel*), in septic patients (*inverted triangles, dotted line*) and an age- and gender-matched control group of healthy volunteers (*triangles, solid line*) for the experiments shown in Figure 1. Results are presented as mean ± SEM.

Impaired target site penetration of b-lactams may account for therapeutic failure in patients with septic shock Joukhadar C, Frossard M, Mayer BX, Brunner M, Klein N, Siostrzonek P, Eichler HG, Müller M. Crit Care Med. 2001 Feb;29(2):385-91

6 Patienten pro Gruppe, MIC im Gewebe nicht erreicht, obwohl ausreichend Plasmakonzentration

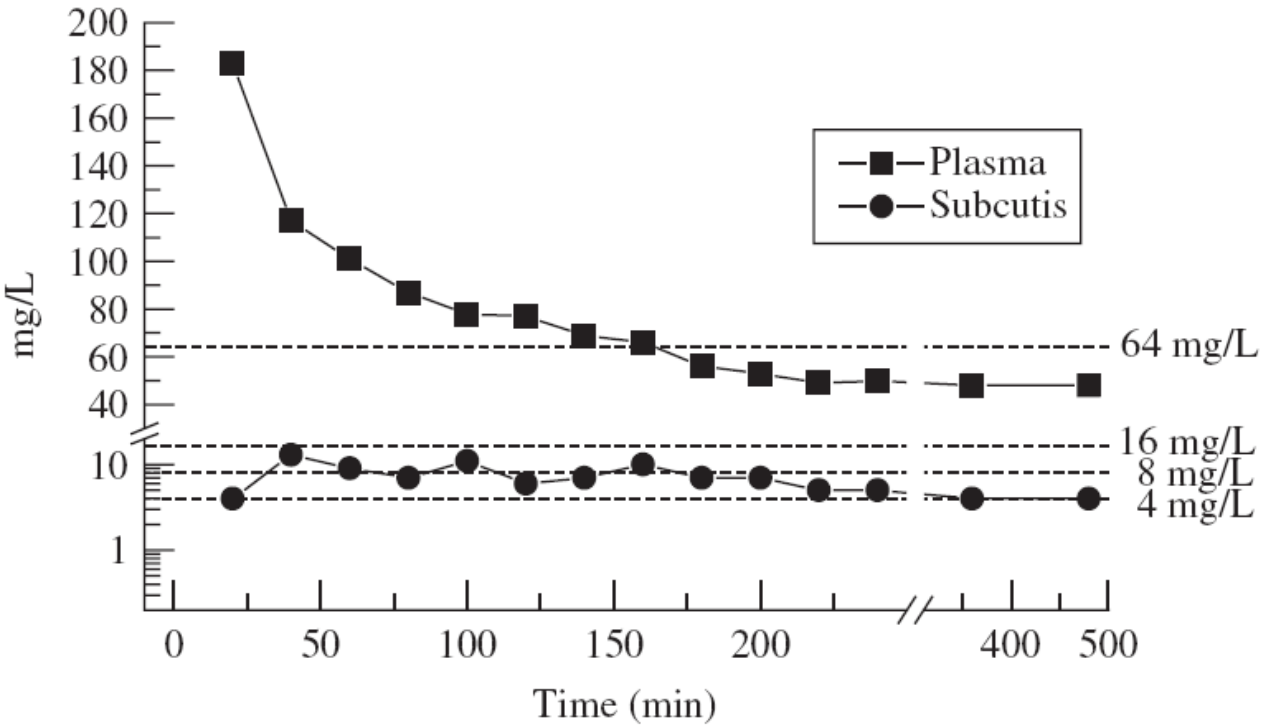
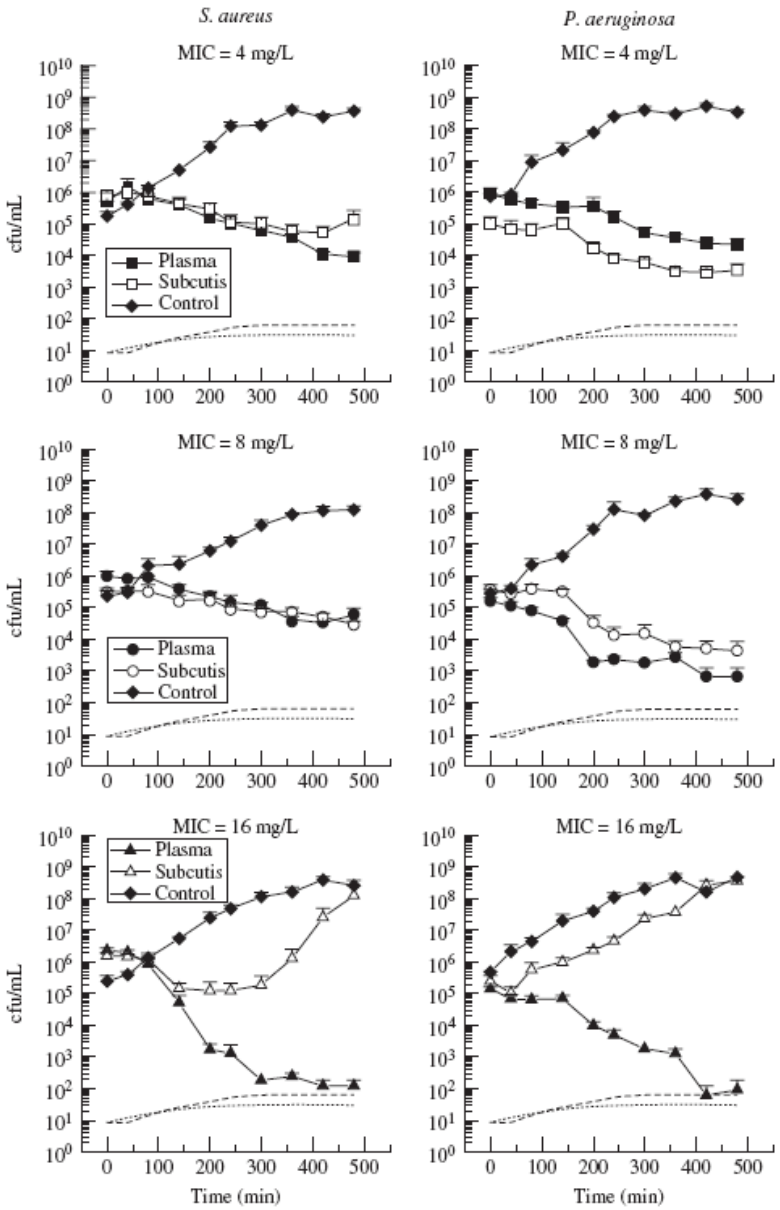


Figure 1. Concentration-versus-time profiles of piperacillin simulated for plasma (squares) and subcutis (circles) in the *in vivo* PK/*in vitro* PD model. MICs for employed pathogens and the NCCLS breakpoint are indicated by horizontal dashed lines.

Zeitlinger. J Antimicrob Chemother. 2005


S. aureus
P. aeruginosa
MIC = 4 mg/L
MIC = 8 mg/L
MIC = 16 mg/L
cfu/mL
Plasma
Subcutis
Control
Time (min)

Plasma concentrations might lead to overestimation of target site activity of piperacillin in patients with sepsis

M. A. Zeitlinger[1], B. M. Erovic[2], R. Sauermann[1], A. Georgopoulos[3], M. Müller[1] and C. Joukhadar[1,3]*

Our in vitro simulation showed that bacterial killing may be effective in severely ill patients despite relatively low concentrations of piperacillin at the target site.

Journal of Antimicrobial Chemotherapy (2005) **56**, 703–708

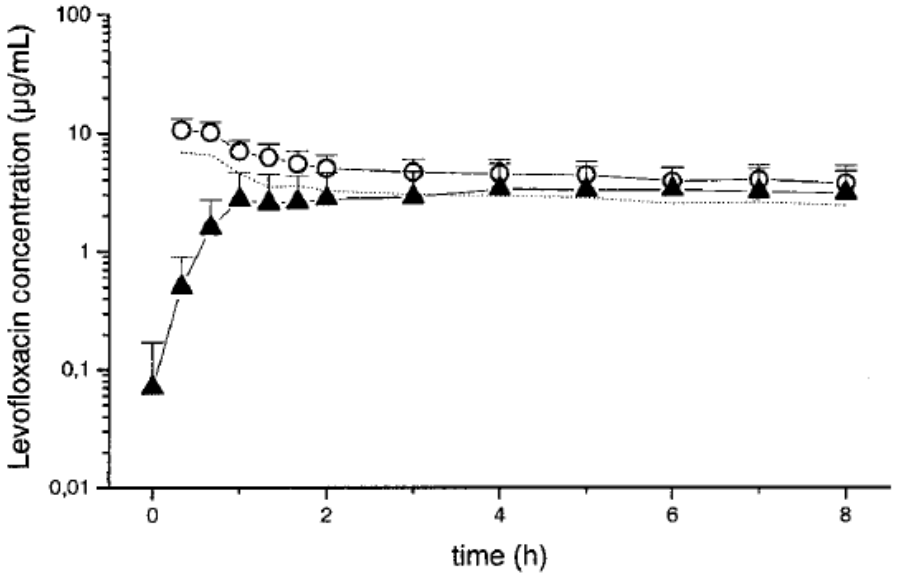


FIG. 1. Mean concentration-versus-time profiles of levofloxacin for total (open circles) and free (dotted line) concentrations in plasma and skeletal muscle tissue (triangles) following administration of 500 mg to patients with sepsis ($n = 7$). Data are presented as means ± standard deviations.

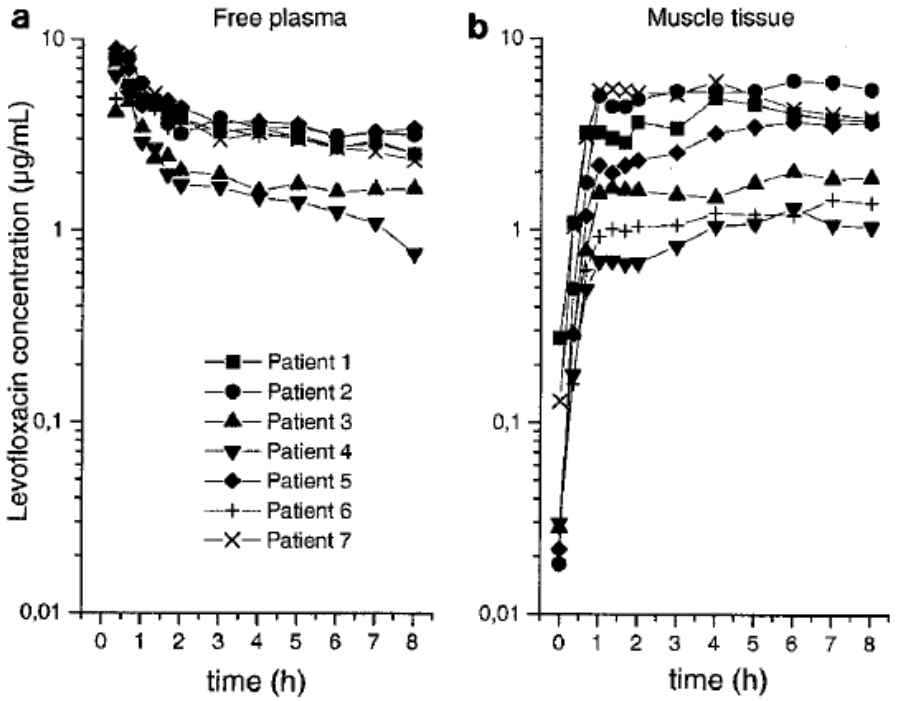
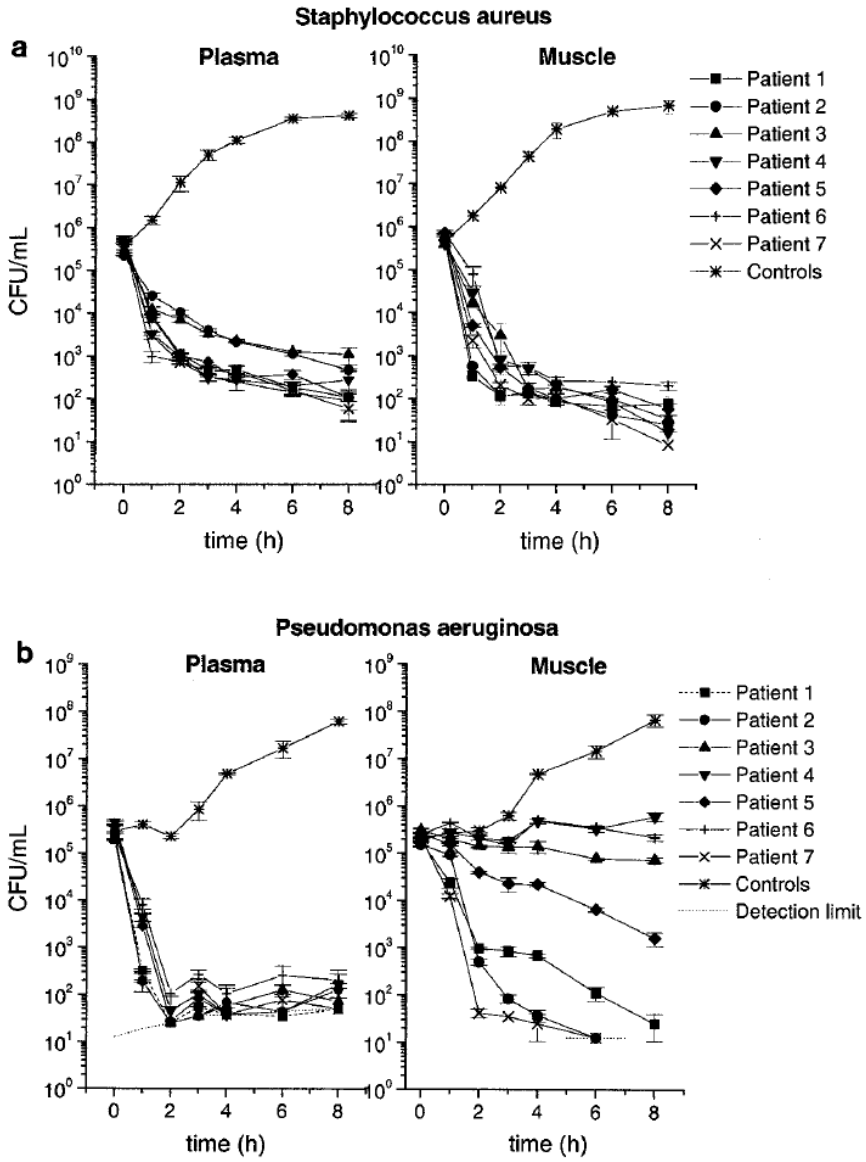


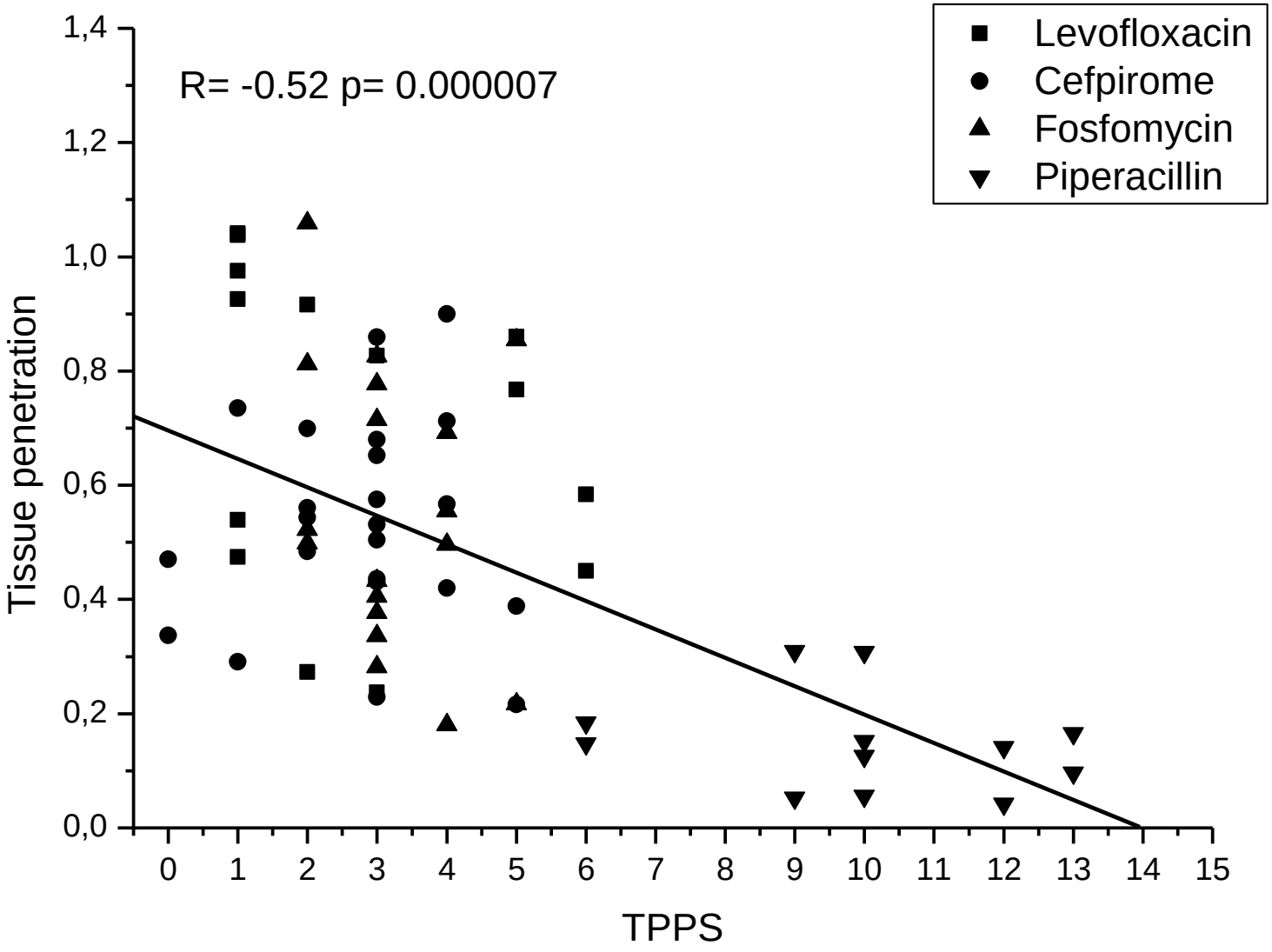
FIG. 2. Individual pharmacokinetic concentration-versus-time profiles of free levofloxacin in plasma (a) and skeletal muscle tissue (b).


Staphylococcus aureus
a
Plasma
Muscle
CFU/mL
time (h)
time (h)
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Patient 7
Controls
Pseudomonas aeruginosa
b
Plasma
Muscle
CFU/mL
time (h)
time (h)
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Patient 7
Controls
Detection limit

Tissue Penetration Prediction Score (TPPS) for sepsis:

POINTS	0	1	2	3	4	5
SaO_2 (%)	>98	>96	>94	>92	>90	≤90
Lactate (mM/L)	<1	<1.5	<2	<2.5	<4	≥4
Norepinephrine ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0	<0.2	<0.3	<0.4	<0.5	≥0.5

Zeitlinger et al. 2007

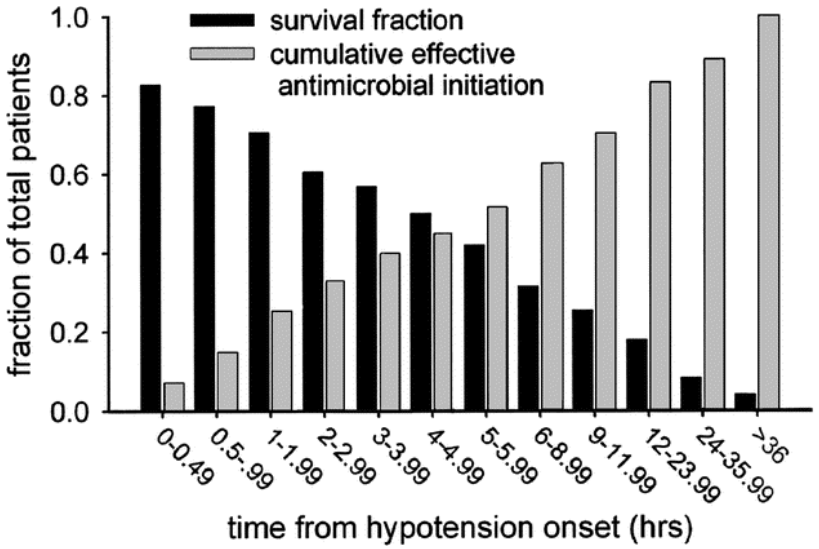


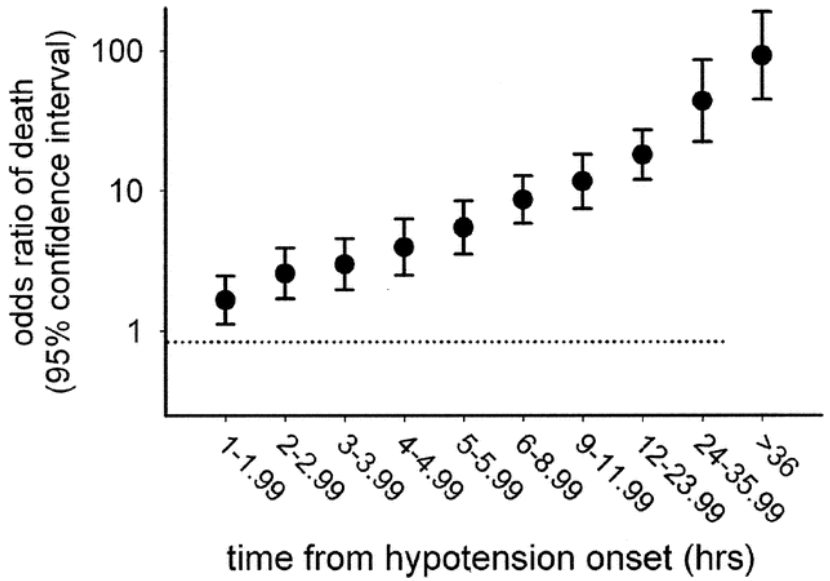
Zeitlinger et al. 2007

Zirka 40% der Patienten, die mit einer Standarddosierung von Vancomycin 2 mal 1g erreichen keine wirksamen Vancomycinlungenkonzentrationen(>4mg/l).
Die Konzentrationen in den pulmonalen Kompartimenten erreichen nur zirka 20% der korrespondierenden Plasmaspiegel und ist damit weit unter der MIC.

Die Konzentration von Linezolid in den Lungenkompartimenten erreicht mit der Dosierung von 2x 600 mg >100% vom Plasmaspiegel.

LAMER ET AL. ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 1993, p. 281-286





Kumar et al: Crit Care Med, Volume 34(6).June 2006.1589-1596

Universitätsklinikum Essen
Klinik für Anästhesiologie und Intensivmedizin

Mayo Clin Proc. 2012 Apr;87(4):349-63.

Meta-analysis of randomized controlled trials of vancomycin for the treatment of patients with gram-positive infections: focus on the study design.

Vardakas KZ, Mavros MN, Roussos N, Falagas ME.

Alfa Institute of Biomedical Sciences, Athens, Greece.

Abstract

OBJECTIVE: To study the effectiveness and safety of **vancomycin** compared with that of other antibiotics for the treatment of gram-positive infections.

METHODS: Major electronic databases were searched. Data from published randomized controlled trials (January 1, 1950, to September 15, 2011) were pooled using a meta-analytic method.

RESULTS: Fifty-three trials comparing **vancomycin** with **linezolid**, daptomycin, quinupristin-dalfopristin, tigecycline, ceftaroline, ceftobiprole, telavancin, teicoplanin, iclaprim, and dalbavancin were included in the meta-analysis. Individual antibiotics were as effective as **vancomycin**, except for **linezolid**, which was more effective than **vancomycin** for the treatment of skin and soft tissue infections (odds ratio [OR], 1.61; 95% confidence interval [CI], 1.07-2.43). Comparators were as effective as **vancomycin** in the intent-to-treat population (OR, 1.08; 95% CI, 0.98-1.18) but were more effective in the clinically evaluable population (OR, 1.14; 95% CI, 1.02-1.27) when all infections were pooled. When available data from all trials were pooled, no differences were noted when patients with febrile neutropenia (OR, 1.07; 95% CI, 0.82-1.39), pneumonia (OR, 1.10; 95% CI, 0.87-1.37), bacteremia (OR, 1.05; 95% CI, 0.76-1.45), and skin and soft tissue infections (OR, 1.11; 95% CI, 0.89-1.39) were studied. Comparators were more effective in open-label (OR, 1.28; 95% CI, 1.08-1.50) but not in double-blind trials (OR, 1.04; 95% CI, 0.90-1.20). Total adverse events attributed to studied antibiotics (OR, 1.07; 95% CI, 0.90-1.28) and patients withdrawn from trials (OR, 0.86; 95% CI, 0.68-1.09) were similar in the compared groups. Mortality was not different between **vancomycin** and comparator antibiotics when all trials were included in the analysis (OR, 1.09; 95% CI, 0.96-1.23). Comparators were associated with higher mortality in open-label (OR, 1.27; 95% CI, 1.05-1.54) but not double-blind trials (OR, 0.96; 95% CI, 0.80-1.14).

CONCLUSION: On the basis mainly of data from open-label trials, **vancomycin** is a treatment choice that is as effective as other available antibiotics for patients with gram-positive infections. Study design seems to make a major contribution to the outcome.

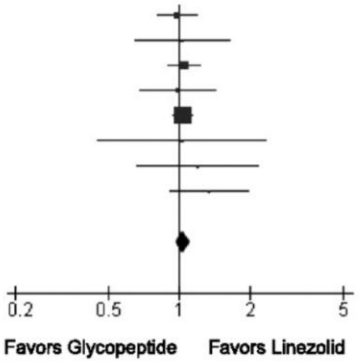
From: Linezolid vs Glycopeptide Antibiotics for the Treatment of Suspected Methicillin-Resistant Staphylococcus aureus Nosocomial Pneumonia: A Meta-analysis of Randomized Controlled Trials

CHEST. 2011;139(5):1148-1155. doi:10.1378/chest.10-1556

A

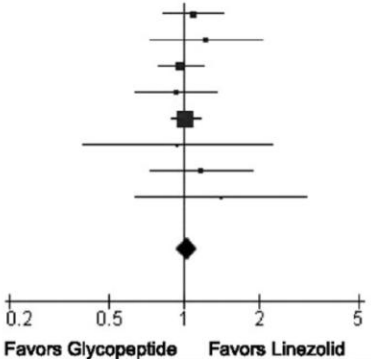
Study or Subgroup	#success / total		Risk Ratio (95% CI)
	Linezolid	Glycopeptide	
Clinical Success, test of cure, clinically evaluable			
Rubinstein et al. 2001	71 / 107	62 / 91	0.97 (0.80, 1.18)
Stevens et al. 2002	20 / 39	16 / 32	1.03 (0.65, 1.63)
Wunderink et al. 2003	114 / 168	111 / 171	1.05 (0.90, 1.22)
Cepeda et al 2004	23 / 43	30 / 55	0.98 (0.68, 1.42)
Wilcox et al. 2004	51 / 53	52 / 56	1.04 (0.95, 1.13)
Kohno et al. 2007	11 / 34	6 / 19	1.02 (0.45, 2.33)
Wunderink et al. 2008	13 / 23	9 / 19	1.19 (0.66, 2.16)
Lin et al. 2008	19 / 26	18 / 33	1.34 (0.91, 1.98)
Total, Clinical Success, evaluable subjects, test of cure	322 / 493	304 / 476	1.04 (0.97, 1.11)
Heterogeneity χ^2 2.39, p=0.94, I^2=0%			
Test for overall effect, p=0.28			

Random Effect, Risk ratio (95% CI)



B

Clinical Success, test of cure, intention to treat			
Rubinstein et al. 2001	71 / 203	62 / 193	1.09 (0.82, 1.44)
Stevens et al. 2002	20 / 50	26 / 49	1.23 (0.72, 2.07)
Wunderink et al. 2003	114 / 321	111 / 302	0.97 (0.78, 1.19)
Cepeda et al 2004	23 / 47	30 / 57	0.93 (0.63, 1.36)
Wilcox et al. 2004	51 / 57	52 / 59	1.02 (0.89, 1.16)
Kohno et al. 2007	11 / 51	6 / 26	0.93 (0.39, 2.24)
Lin et al. 2008	19 / 38	18 / 42	1.17 (0.73, 1.87)
Wunderink et al. 2008	13 / 74	9 / 72	1.41 (0.64, 3.08)
Total, Clinical Success, test of cure, intention to treat	322/841	304/800	1.02 (0.93, 1.12)
Heterogeneity χ^2 2.20, p=0.95, I^2=0%			
Test for overall effect, p=0.63			



Welche klinische Relevanz hat die Betrachtung der Gewebepenetration bei der schweren Infektion?

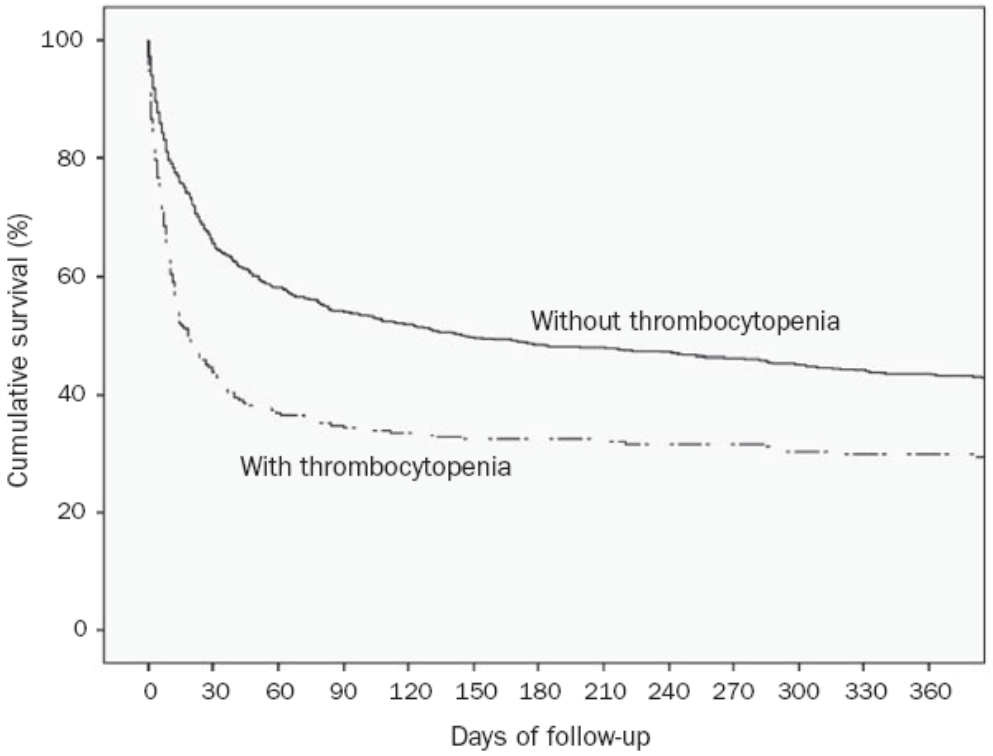
?

Welche Gewebkonzentration brauchen wir bei den individuell verschiedenen immunologischen Bedingungen?
Welche Biomarker könnten dabei helfen?

Platelets display potent antimicrobial activity and release human beta-defensin 2

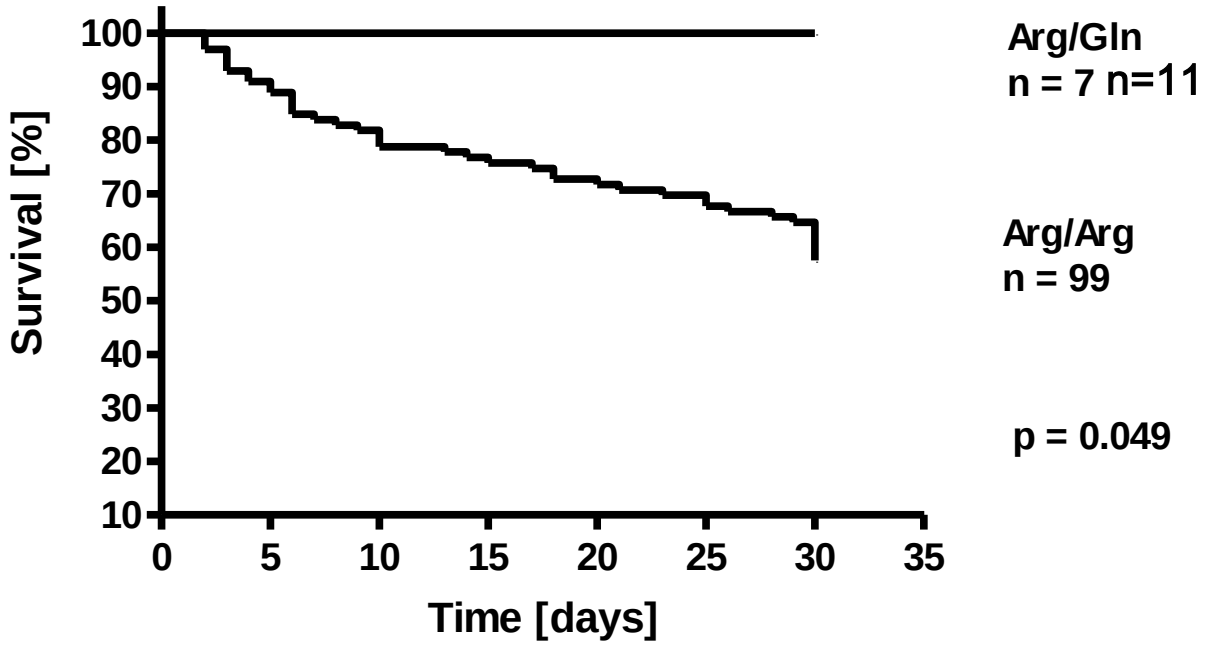
Platelets.2012;23(3):217-23.

Human neutriphil alpha defensins induce formation of fibrinogen and thrombospondin-1-amyloid-like structures and activate platelets via glycoprotein IIb/III.Horn M, Bertling A, Brodde MF, Müller A, Roth J, Van Aken H, Jurk K, Heilmann C, Peters G, Kehrel BE. J Thromb Haemost. 2012 Apr;10(4):647-61. doi: 10.1111/j.1538-7836.2012.04640



		Days												
		0	30	60	90	120	150	180	210	240	270	300	330	365
Without	No. of patients	817	541	473	440	422	405	395	391	385	377	368	361	353
	Deaths	0	276	344	377	395	412	422	426	432	440	449	456	464
With	No. of patients	235	103	87	81	79	76	76	75	74	74	71	70	70
	Deaths	0	132	148	154	156	159	159	160	161	161	164	165	165

30 day survival of ARDS Patients with regard to the Factor V Leiden polymorphism

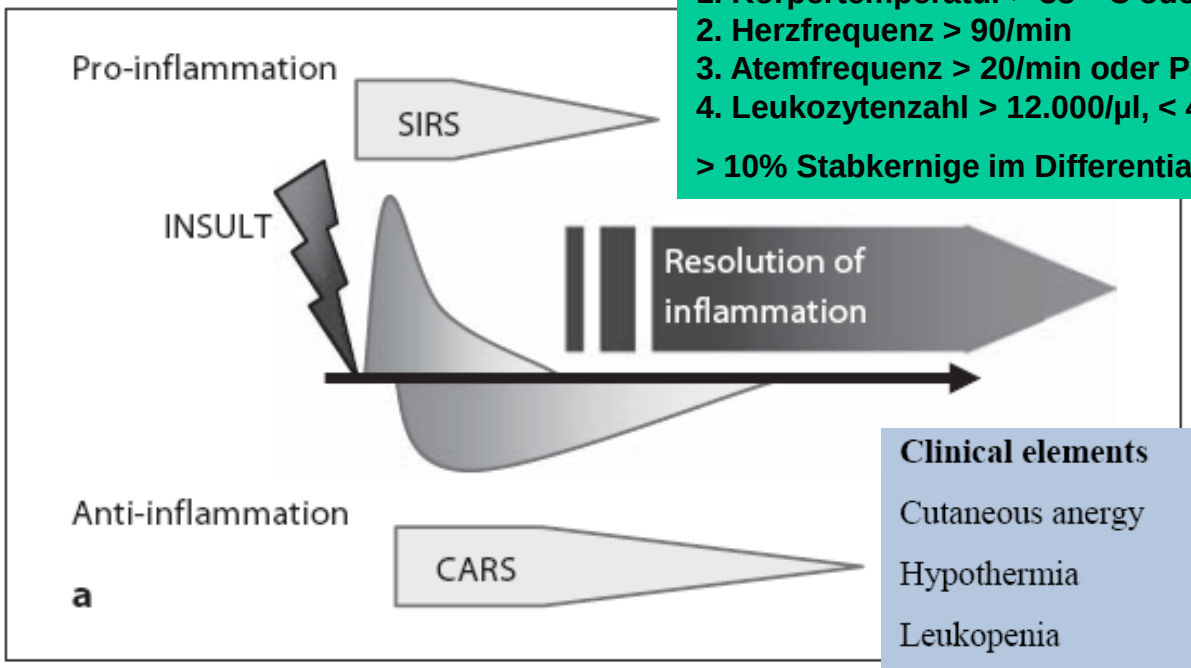


Adamzik M, et al.: Factor V Leiden mutation is associated with improved 30-day survival in patients with acute respiratory distress syndrome. Crit Care Med 2008; 36: 1776-9

Protein C inhibitor--a novel **antimicrobial** agent. Malmström E, Mörgelin M, Malmsten M, Johansson L, Norrby-Teglund A, Shannon O, Schmidtchen A, Meijers JC, Herwald H. PLoS Pathog. 2009 Dec;5(12):e1000698.

1. Körpertemperatur > 38° C oder < 36° C
2. Herzfrequenz > 90/min
3. Atemfrequenz > 20/min oder PaCO2 < 32 mmHg
4. Leukozytenzahl > 12.000/µl, < 4000/µl oder

> 10% Stabkernige im Differentialblutbild



Clinical elements
Cutaneous anergy
Hypothermia
Leukopenia
Susceptibility to infection
Failure to clear infection

Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS)

Bone RC.
Ann Intern Med. 1996 Oct 15;125(8):680-7.

International Immunopharmacology 11 (2011) 444–448

Contents lists available at ScienceDirect

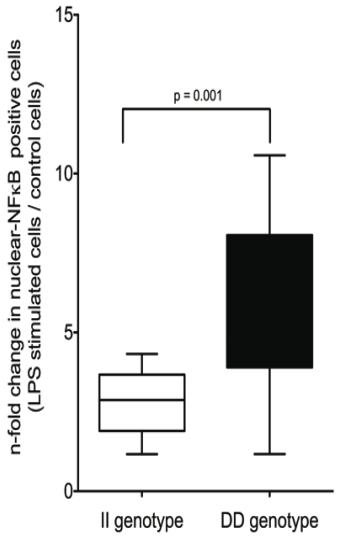
International Immunopharmacology

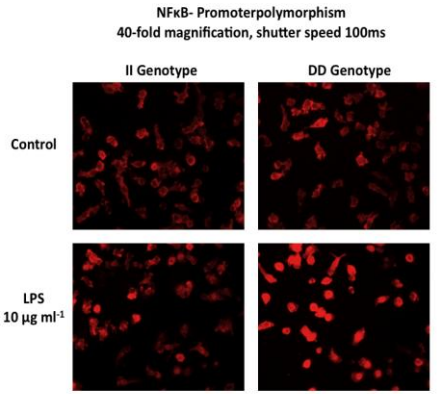
journal homepage: www.elsevier.com/locate/intimp

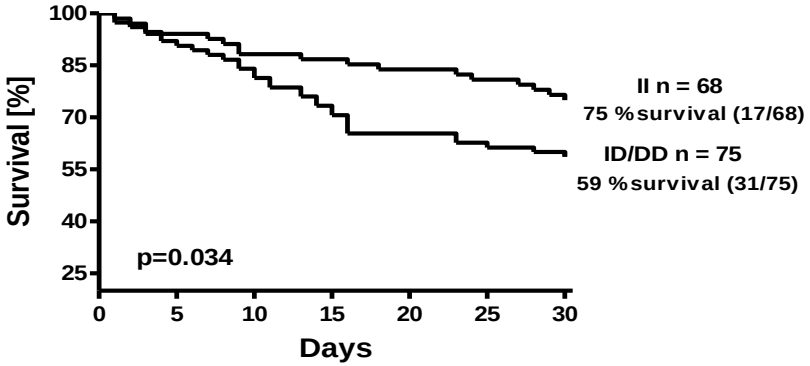
IL-5 release of $CD4^+$ non-effector lymphocytes is increased in COPD — modulating effects of moxifloxacin and dexamethasone

Katharina Schild [a], Jürgen Knobloch [a], Yakup Yakin [a], David Jungck [a], Katja Urban [a], Katja Müller [a], Andrea Koch [a,b,*]

[a] Department of Pneumology, Clinic III for Internal Medicine, University of Cologne, Germany
[b] Medical Clinic III for Pneumology, Allergology, Sleep Medicine, Bergmannsheil University Hospital, Bochum, Germany







Adamzik et al. Anesthesiology 2012

Bei Intensivpatienten unterscheidet sich die freie Serumkonzentration der Antibiotika erheblich von der Gewebekonzentration.

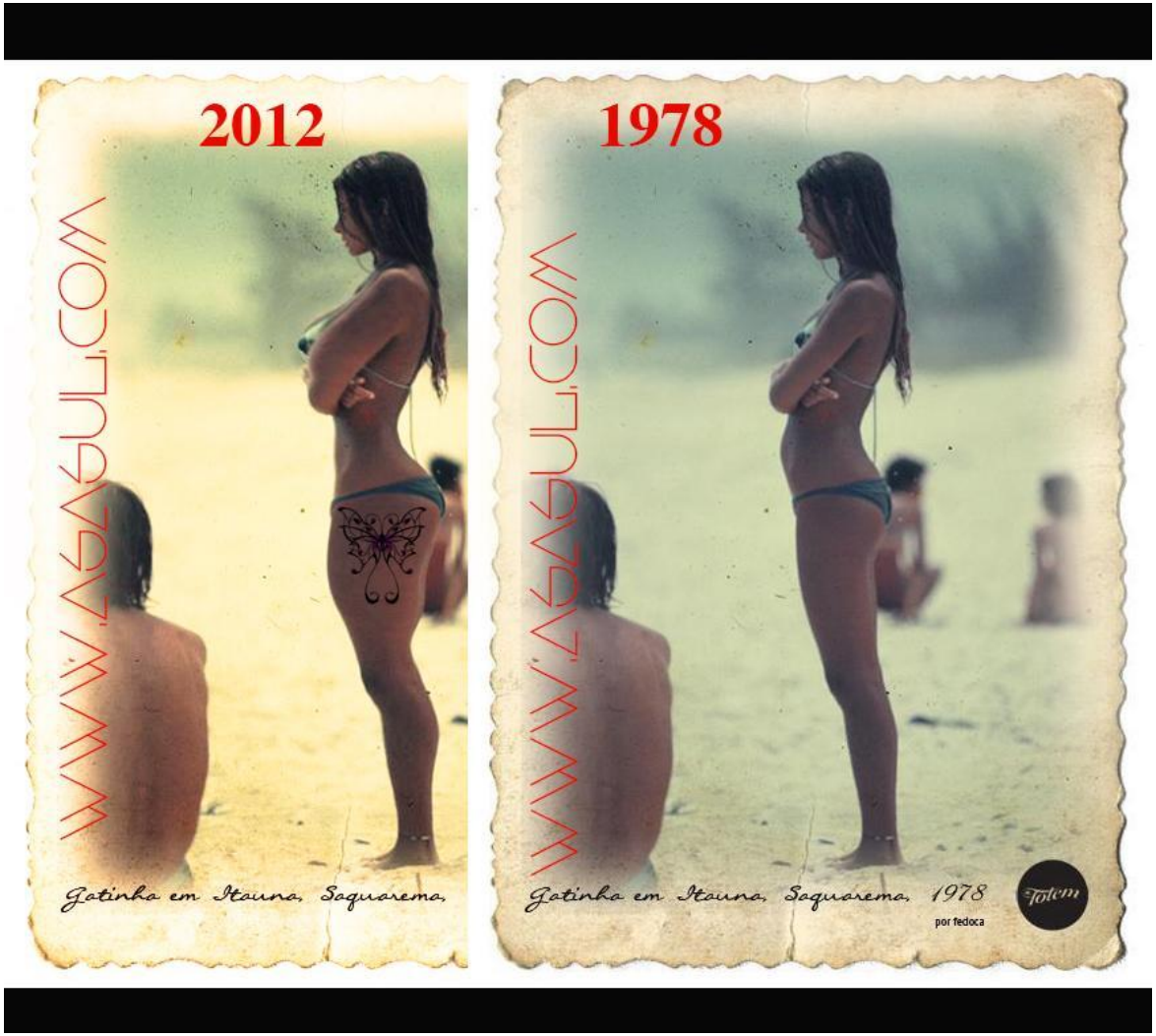
Die Gewebepenetration zeigt eine große Interindividuelle Variabilität und lässt sich nicht verallgemeinern.

Scores, welche die Makro und Mikrozirkulation bewerten, könnten helfen die Gewebepenetration voraus zu sagen, sollte aber durch immunologische Einflussgrößen erweitert werden.

Die Effektive Gewebekonzentration ist bis heute eine unbekannte Konstante.

Eine Assoziation zwischen Gewebepenetration und Outcome ist bis heute bei Patienten mit der Notwendigkeit zur Intensivtherapie noch nicht gezeigt worden und muss Gegenstand aktueller Forschung werden.

Vielen Dank für Ihre Aufmerksamkeit



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