

**ENTSCHEIDEND IST DER THERAPIEERFOLG**  
 "Rational Documents" als Grundlage für die EUCAST-Breakpoints

Einladung zur Veranstaltung  
**EUCAST reloaded 1.0**  
 Follow-up Workshop

**FLORIAN THALHAMMER**  
 UNIVERSITÄTSKLINIK FÜR INNERE MEDIZIN  
 Klinische Abteilung für Infektionen und Tropenmedizin  
 ALLGEMEINES KRANKENHAUS & MEDIZINISCHE UNIVERSITÄT WIEN

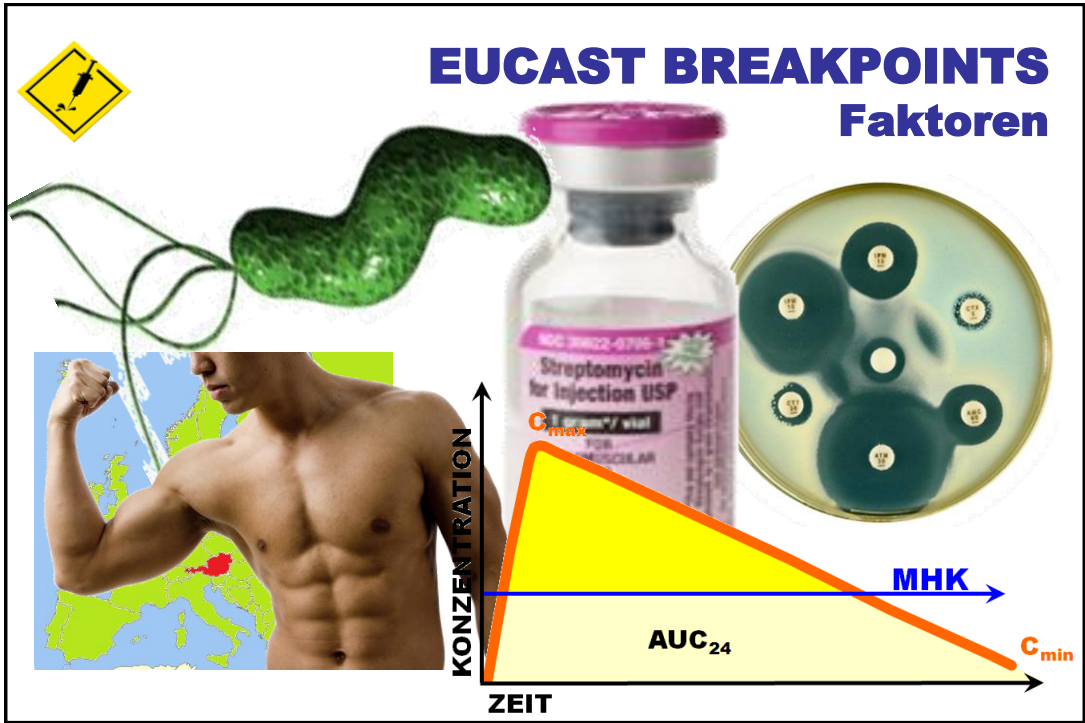
KONZENTRATION  
 ZEIT

$C_{max}$   
 MHK  
 $C_{min}$

## **EUCAST BREAKPOINTS**

### **Europa ist anders**

- europäische min-max-Dosierungen
- EMA-Indikationen
- Outcome & Pharmakodynamik
- Resistenzentwicklung
- Konsens, keine Abstimmung
- unabhängig von der Industrie
- frei zugänglich



**EUCAST BREAKPOINTS  
EUCAST Homepage**

**EUCAST** EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING  
European Society of Clinical Microbiology and Infectious Diseases

Home Contact Sitemap

**The European Committee on Antimicrobial Susceptibility Testing – EUCAST**

search term  Search  
QUICK NAVIGATION

**News**

- Preparedness of manufacturers - update 2011-03-07
- Frequently Asked Questions - update 2011-02-28
- Consultation on antifungals - consultation Feb 24 - March 31:
  - Amfotericin B
  - Anidulafungin
  - Posaconazole
- Clinical breakpoint tables v 1.3 - published 2011-01-05
- Note to European laboratories - update 2010-12-01
- bioMerieux Vitek2 pip/tazo-warning - published 2010-10-22

[www.eucast.org](http://www.eucast.org) – 12.3.2011



# EUCAST BREAKPOINTS Rational Documents

*Staphylococcus* spp.

EUCAST Clinical Breakpoint Table v. 1.3 2011-01-05

Penicillins <sup>1</sup>	MIC breakpoint (mg/L)		Disk content (µg)	Zone diameter breakpoint (mm)		Notes Numbers for comments on MIC breakpoints Letters for comments on disk diffusion
	S ≤	R >		S ≥	R <	
	0.125 <sup>1</sup>	0.125 <sup>1,2</sup>	1 unit	26 <sup>3,8</sup>	26 <sup>3,8</sup>	A. Most staphylococci are penicillinase-producers. The benzylpenicillin breakpoint will mostly, but not unequivocally, separate beta-lactamase producers from non-producers. Isolates positive for beta-lactamase are resistant to benzylpenicillin, phenoxymethylpenicillin, amino-, carboxy- and ureidopenicillins. Isolates negative for beta-lactamase and susceptible to cefoxitin (cefoxitin is used to screen for "methicillin resistance") can be reported susceptible to these drugs. Isolates positive for beta-lactamase and susceptible to cefoxitin are susceptible to penicillin-beta-lactamase inhibitor combinations and penicillinase-resistant penicillins (oxacillin, cloxacillin, dicloxacillin and flucloxacillin). Isolates resistant to cefoxitin are methicillin resistant and resistant to beta-lactam agents, including beta-lactamase inhibitor combinations, except for cephalosporins with approved anti-MRSA activity and clinical breakpoints.
Benzylpenicillin	0.125 <sup>1</sup>	0.125 <sup>1,2</sup>	1 unit	26 <sup>3,8</sup>	26 <sup>3,8</sup>	B. Isolates with inhibition zones above the breakpoint and a fuzzy zone edges can be reported susceptible to benzylpenicillin.
Ampicillin	Note <sup>3</sup>	Note <sup>3</sup>	2	15 <sup>6,8</sup>	15 <sup>6,8</sup>	C. Breakpoints relate to <i>S. saprophyticus</i> only.
Ampicillin-sulbactam	Note <sup>3</sup>	Note <sup>3</sup>		Note <sup>6</sup>	Note <sup>6</sup>	
Amoxicillin	Note <sup>3</sup>	Note <sup>3</sup>		Note <sup>6</sup>	Note <sup>6</sup>	
Amoxicillin-clavulanate	Note <sup>3</sup>	Note <sup>3</sup>		Note <sup>6</sup>	Note <sup>6</sup>	
Piperacillin	Note <sup>3</sup>	Note <sup>3</sup>		Note <sup>6</sup>	Note <sup>6</sup>	
Piperacillin-tazobactam	Note <sup>3</sup>	Note <sup>3</sup>		Note <sup>6</sup>	Note <sup>6</sup>	
Ticarcillin	Note <sup>3</sup>	Note <sup>3</sup>		Note <sup>6</sup>	Note <sup>6</sup>	
Ticarcillin-clavulanate	Note <sup>3</sup>	Note <sup>3</sup>		Note <sup>6</sup>	Note <sup>6</sup>	
Phenoxymethylpenicillin	Note <sup>3</sup>	Note <sup>3</sup>		Note <sup>6</sup>	Note <sup>6</sup>	
Oxacillin <sup>4</sup>	Note <sup>1,2</sup>	Note <sup>1,2</sup>		Note <sup>6</sup>	Note <sup>6</sup>	Z. <i>S. aureus</i> and <i>S. lugdunensis</i> with oxacillin MIC values >2 mg/L, are mostly methicillin resistant due to the presence of the <i>mecA</i> gene. The corresponding oxacillin MIC for coagulase-negative staphylococci is =0.25 mg/L.
Cloxacillin	Note <sup>3</sup>	Note <sup>3</sup>		Note <sup>6</sup>	Note <sup>6</sup>	
Dicloxacillin	Note <sup>3</sup>	Note <sup>3</sup>		Note <sup>6</sup>	Note <sup>6</sup>	
Flucloxacillin	Note <sup>3</sup>	Note <sup>3</sup>		Note <sup>6</sup>	Note <sup>6</sup>	
Mecillinam (uncomplicated UTI only)	-	-		-	-	

www.eucast.org



# EUCAST BREAKPOINTS Rational Documents

## Antimicrobial wild type distributions of microorganisms

### Search

Method:  MIC  Disk diffusion

Antimicrobial: Benzylpenicillin

Species: Species...

Disk content: Disk content...

Antimicrobial: Benzylpenicillin (Method: MIC)

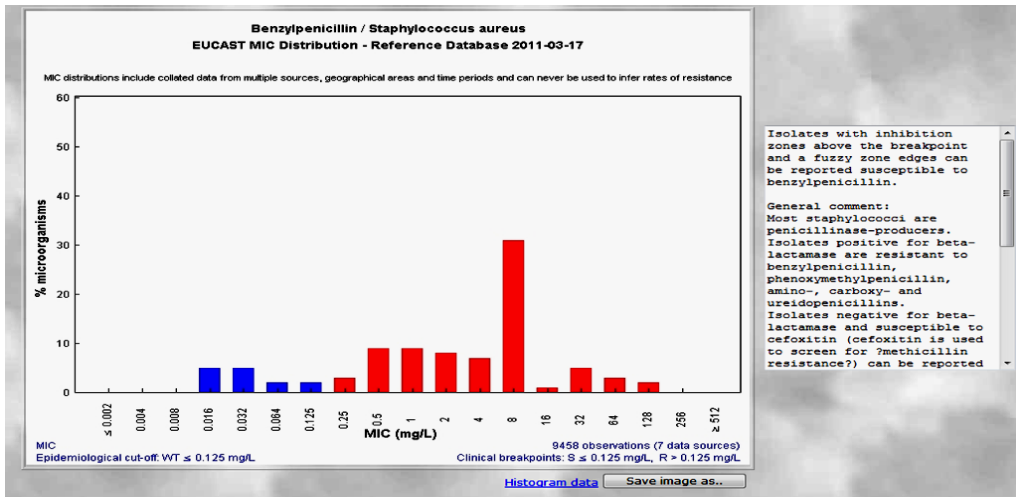
MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	S ≤	R >	ECOFFS
<i>Bacteroides fragilis</i>	0	0	0	0	0	0	0	0	0	0	1	19	42	7	0	1	3	2	0	0.25	0.5	ND
<i>Bacteroides fragilis sensu stricto</i>	0	0	0	0	0	0	0	1	1	11	10	51	91	168	79	105	21	24	19	0.25	0.5	ND
<i>Bacteroides thetaiotaomicron</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	7	0	0.25	0.5	ND
<i>Clostridium butyricum</i>	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0.25	0.5	ND
<i>Clostridium difficile</i>	0	0	0	1	2	2	56	426	1054	368	264	43	16	5	0	0	0	0	0	ND	ND	ND
<i>Clostridium perfringens</i>	0	0	15	23	23	18	6	2	0	1	0	0	0	0	0	0	0	0	0	0.25	0.5	0.125
<i>Clostridium ramosum</i>	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0.25	0.5	ND
<i>Clostridium septicum</i>	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.25	0.5	ND
<i>Clostridium sporosaeans</i>	0	0	0	0	1	0	0	3	1	0	0	0	0	0	0	0	0	0	0	0.25	0.5	ND
<i>Clostridium spp</i>	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0.25	0.5	ND
<i>Corynebacterium jeikeium</i>	0	0	0	1	0	1	0	1	0	1	3	9	0	1	48	0	0	0	0	ND	ND	ND
<i>Enterococcus avium</i>	0	0	0	0	0	0	1	15	28	10	3	2	14	29	0	0	0	0	0	ND	ND	ND
<i>Enterococcus casseliflavus</i>	0	0	0	1	0	0	0	26	15	8	2	1	1	0	5	0	0	0	0	ND	ND	ND
<i>Enterococcus faecalis</i>	0	0	0	7	3	3	8	17	66	513	4899	4031	610	222	46	45	0	1	0	ND	ND	16.0
<i>Enterococcus faecium</i>	0	0	0	2	5	7	66	339	229	53	65	157	292	125	120	3026	88	127	42	ND	ND	16.0
<i>Enterococcus gallinarum</i>	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	S ≤	R >	ECOFFS
<i>Enterococcus gallinarum</i>	0	0	0	0	0	1	0	0	3	32	25	5	3	4	2	26	0	0	0	ND	ND	8.0
<i>Haemophilus influenzae</i>	0	0	0	0	66	106	1198	6558	3528	1359	1195	370	3661	8	32	8	0	13	0	ND	ND	1.0
<i>Haemophilus parainfluenzae</i>	0	0	0	0	7	6	8	5	20	25	21	12	25	0	0	0	0	0	0	ND	ND	ND
<i>Listeria monocytogenes</i>	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	ND	ND	1.0
<i>Neisseria gonorrhoeae</i>	0	1	104	465	183	620	1818	1520	778	1023	365	76	46	424	2	1	0	0	0	0.064	1.0	ND
<i>Neisseria meningitidis</i>	0	4	11	154	770	1677	685	367	116	23	1	0	0	0	0	0	0	0	0	0.064	0.25	0.25
<i>Pentastreptococcus spp</i>	0	1	0	3	2	2	5	3	0	0	0	0	0	0	0	0	0	0	0	0.25	0.5	ND

www.eucast.org



# EUCAST BREAKPOINTS Rational Documents



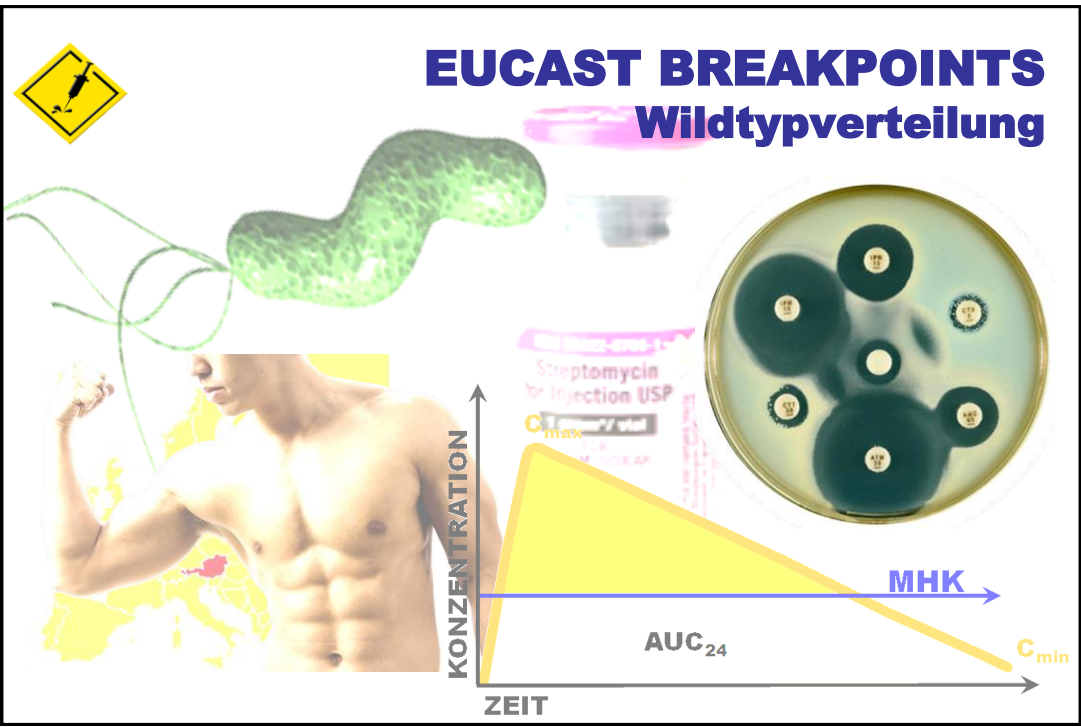
www.eucast.org



# EUCAST BREAKPOINTS Rational documents

1. D	2. N	3. E	4. P	5. P	6. M	8. Clinical breakpoints
Mostly Available	Mostly Available	Mostly Available	Mostly Available	Mostly Available	Mostly Available	<p><b>8. Clinical breakpoints</b></p> <p>Non-species related breakpoints have been determined using PK/Pd data and are independent of MIC distributions of specific species for use only for organisms that do not have specific breakpoints.</p> <p>A 2 log drop in viable Gram-negative organisms in animal model infections requires 40-50% fT-MIC. The 95% confidence interval of those administered by bolus intravenous injection results in an S/I breakpoint of 1 mg/L. The IR breakpoint of 2 mg/L is based on a 2 influenzae and <i>Neisseria</i> spp. susceptible.</p> <p>For <i>Enterobacteriaceae</i> and <i>Moraxella catarrhalis</i> the breakpoints are S <math>\le 1</math> mg/L / R <math>&gt; 2</math> mg/L.</p> <p>For <i>Streptococcus pneumoniae</i> the breakpoints are S <math>\le 0.5</math> mg/L / R <math>&gt; 2</math> mg/L. The S/I breakpoint was reduced to 0.5 mg/L because therapy is necessary for isolates with reduced susceptibility.</p> <p>For <i>Haemophilus influenzae</i>, <i>Neisseria gonorrhoeae</i> and <i>Neisseria meningitidis</i> breakpoints were reduced to S <math>\le 0.12</math> mg/L / R <math>&gt; 0.12</math> mg/L for streptococci other than <i>S. pneumoniae</i> and Groups A, B, C and G to S <math>\le 0.5</math> mg/L / R <math>&gt; 0.5</math> mg/L as isolates with reduced susceptibility are rare or have not been reported and clinical outcome is uncertain.</p> <p>For <i>Staphylococcus</i> spp. susceptibility to cefotaxime is inferred from the ceftiofur susceptibility.</p> <p>For group A, B, C and G streptococci susceptibility to cefotaxime is inferred from the benzylpenicillin susceptibility.</p> <p><i>Pseudomonas aeruginosa</i>, <i>Acinetobacter</i> spp., <i>Enterococcus</i> spp., and anaerobes were considered poor targets for cefotaxime that reason did not receive breakpoints.</p> <p>Clinical qualifications</p> <p>Breakpoints apply to a daily intravenous dose of 1 g x 3 and a high dose of at least 2 g x 3.</p> <p>Dosage</p> <p>For central nervous system infections a high dose is required (Tunkel AR, Schoel WM. Acute meningitis. In: Principles and Practice of Infectious Diseases, Mandell, Bennett, Dolin eds. Elsevier Churchill Livingstone © Edn 2004, pp 1083-1125).</p> <p>Additional comment</p> <p>Cefotaxime: Rationale for the EUCAST clinical breakpoints, version 1.0</p>

www.eucast.org



**EUCAST BREAKPOINTS**  
**Historische Breakpoints**

Cefotaxim bei *Escherichia coli*

		<b>S</b>	<b>R</b>
BSAC	Großbritannien	$\leq 2$	$\geq 4$
CA-SFM	Frankreich	$\leq 4$	$> 32$
CRG	Holland	$\leq 4$	$> 16$
DIN	Deutschland	$\leq 2$	$\geq 16$
NWGA	Norwegen	$\leq 1$	$\geq 32$
SRGA	Schweden	$\leq 0.5$	$\geq 2$



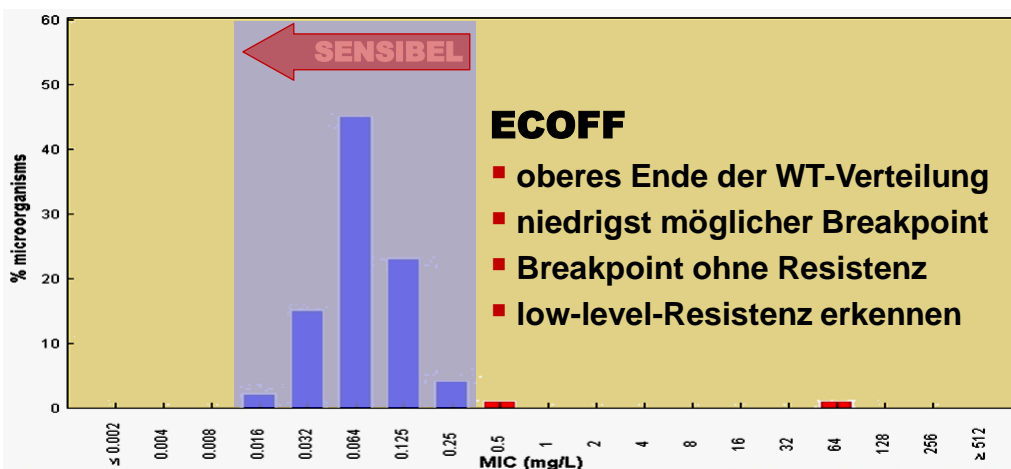
## EUCAST BREAKPOINTS Wildtyp Definition

- Als WT eines Erregers wird jener Stamm bezeichnet, der
  - ohne erworbene Resistenz oder
  - durch Mutation entstandene Resistenzgegen das ausgetestete Antiinfektivum empfindlich ist.
- Für den WT gibt es entsprechende cutt-off Werte
- Der WT eines Erregers kann, muss aber nicht klinisch auf die Antibiotikagabe ansprechen.

[www.eucast.org](http://www.eucast.org)



## EUCAST BREAKPOINTS Wildtyp *E. coli* & Cefotaxim



MHK  
Epidemiologische Grenzen: WT  $\leq 0.25$  mg/L

10829 Beobachtungen (57 Datenquelle)  
Klinische Grenzwerte: S  $\leq 1$  mg/L, R  $> 2$  mg/L

[www.eucast.org](http://www.eucast.org)

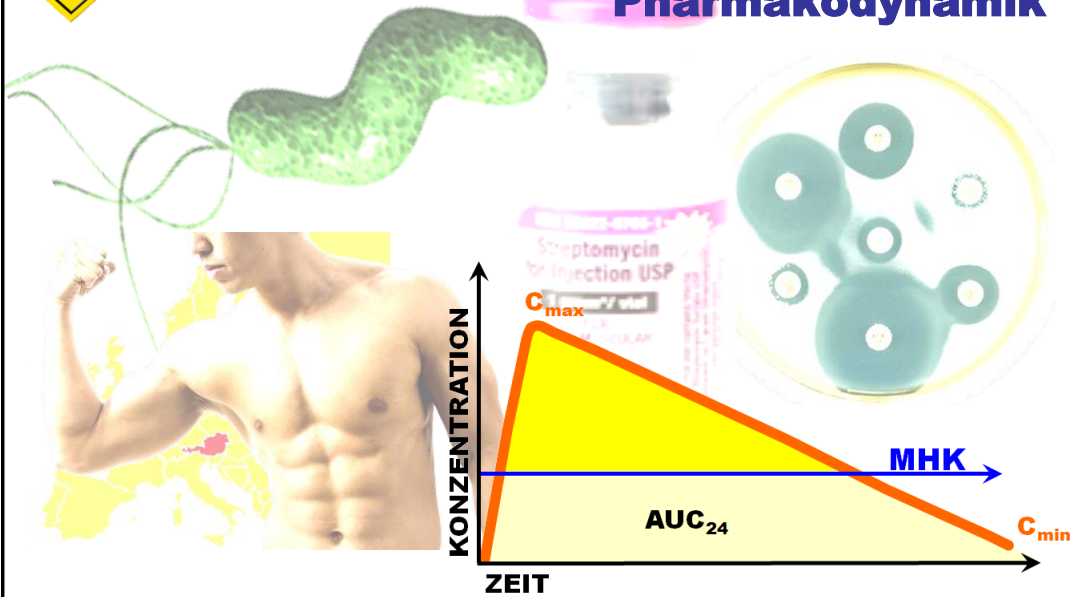


## EUCAST BREAKPOINTS MHK oberhalb des ECOFF

- Qualitätsproblem
  - fehlerhafte Identifikation
  - fehlerhafte MHK-Bestimmung
- Resistenzproblem

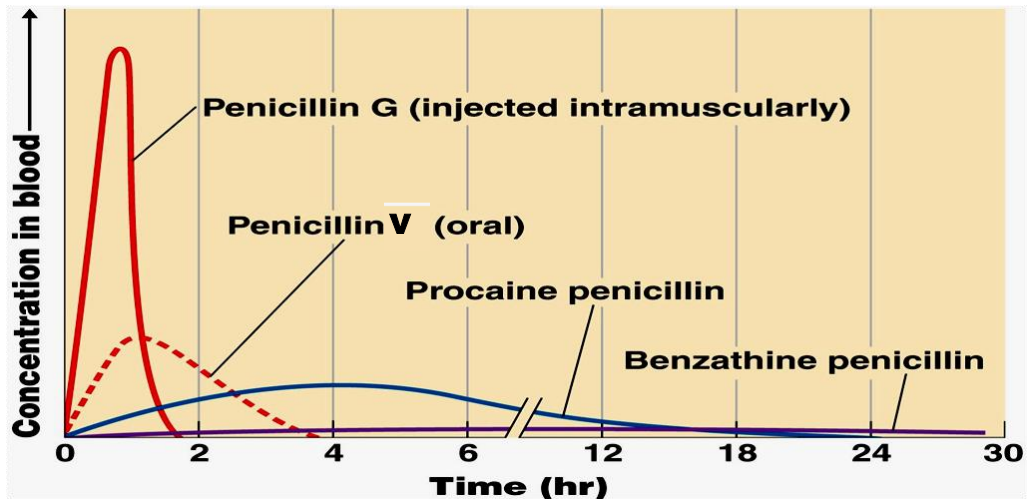


## EUCAST BREAKPOINTS Pharmakodynamik

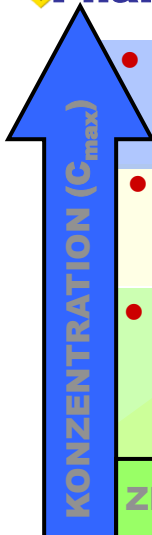




## EUCAST BREAKPOINTS Pharmakologie



## EUCAST BREAKPOINTS Pharmakodynamische Therapieprinzipien



- **Spitzenspiegel/MHK**
  - > Aminoglykoside, Azithromycin
  - > Chinolone, Metronidazol, Daptomycin
- **AUC<sub>24</sub>/MHK**
  - > Fluorchinolone, Tigecyclin
  - > Vancomycin, Daptomycin
- **Zeit oberhalb der MHK**
  - > Penicilline, Cephalosporine
  - > Carbapeneme, Aztreonam, Linezolid
  - > Makrolide, Clindamycin

**KONZ**

je höher, desto besser

**ZEIT**

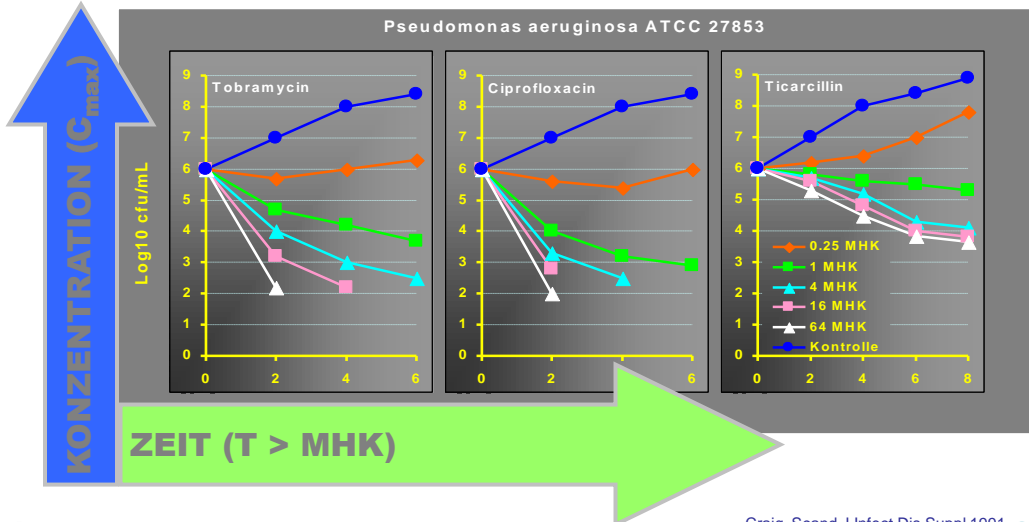
je länger, desto besser





# EUCAST BREAKPOINTS

## Pharmakodynamik im Überblick



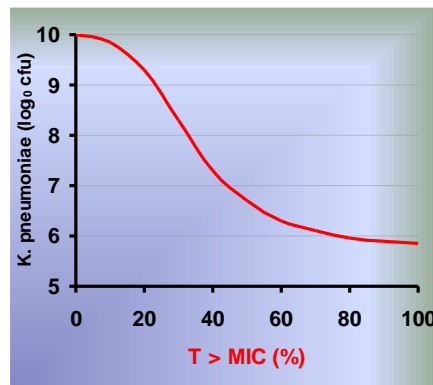
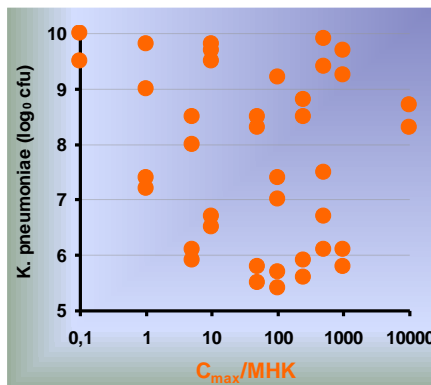
VERSITÄTSKLINIK für INNERE MEDIZIN I - MEDIZINISCHE UNIVERSITÄT WIEN

Craig, Scand J Infect Dis Suppl 1991



# EUCAST BREAKPOINTS

## Zeit vs Konzentration

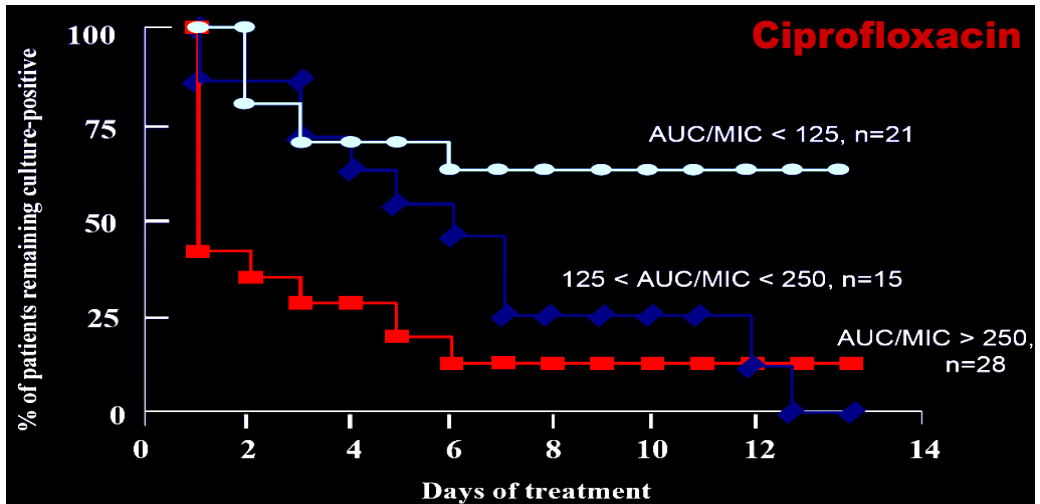


## BETALAKTAM-ANTIBIOTIKA

Craig, Diagn Microbiol Infect Dis 1995



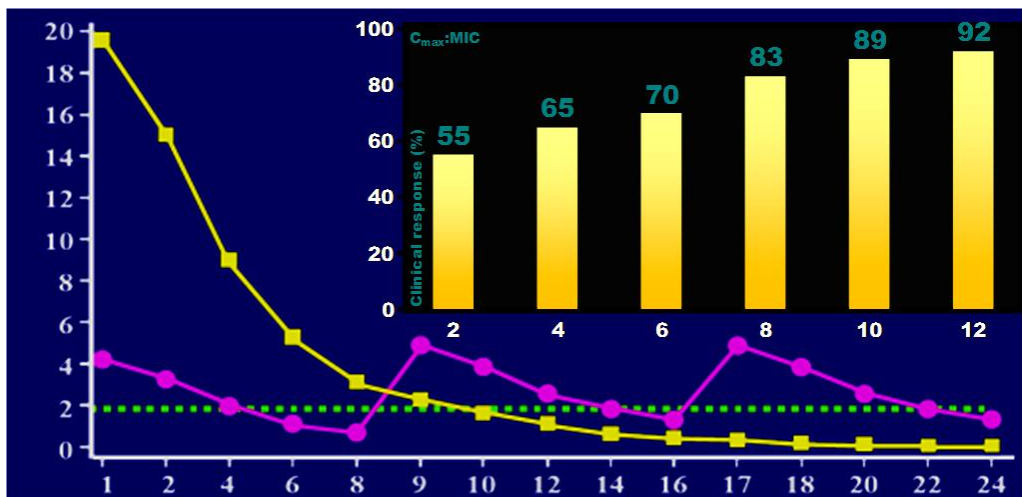
## EUCAST BREAKPOINTS AUC vs MHK



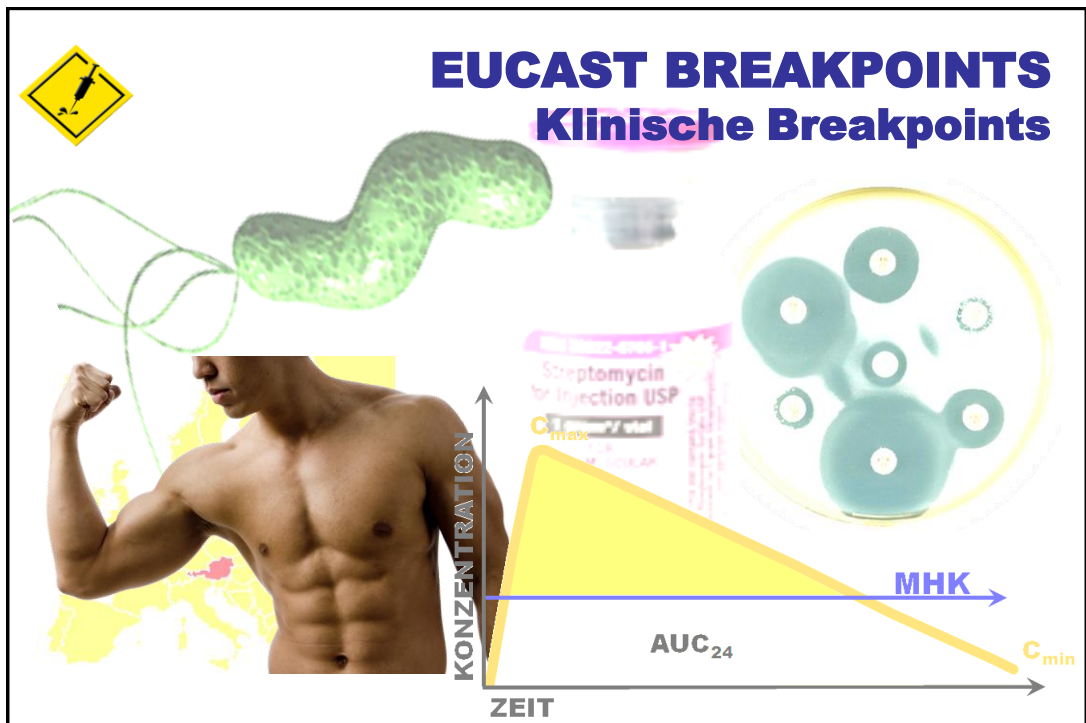
Forrest, Antimicrob Agents Chemother 1993



## EUCAST BREAKPOINTS C<sub>max</sub> vs MHK



Nicolau, Antimicrob Agents Chemother 1995 – Moore, J Infect Dis 1987

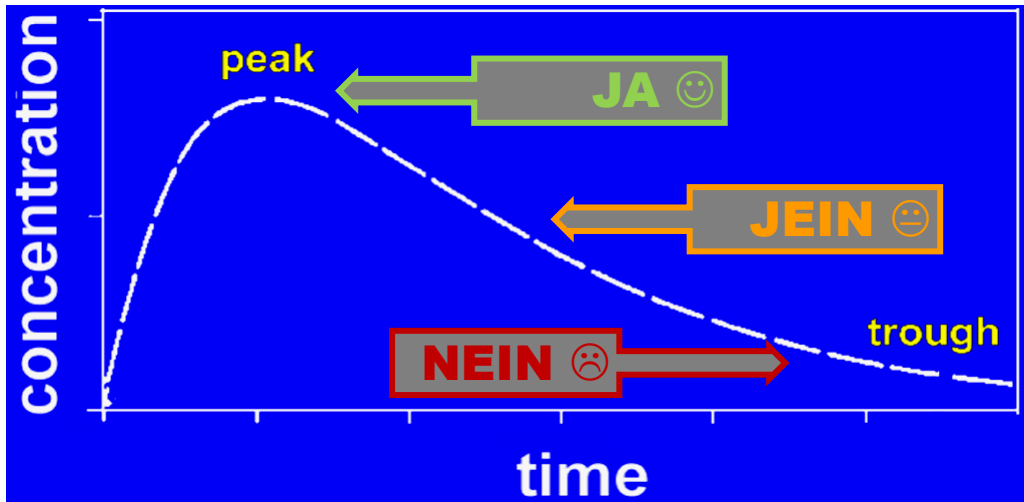


**EUCAST BREAKPOINTS**  
**Bestimmung des klinischen Breakpoints**

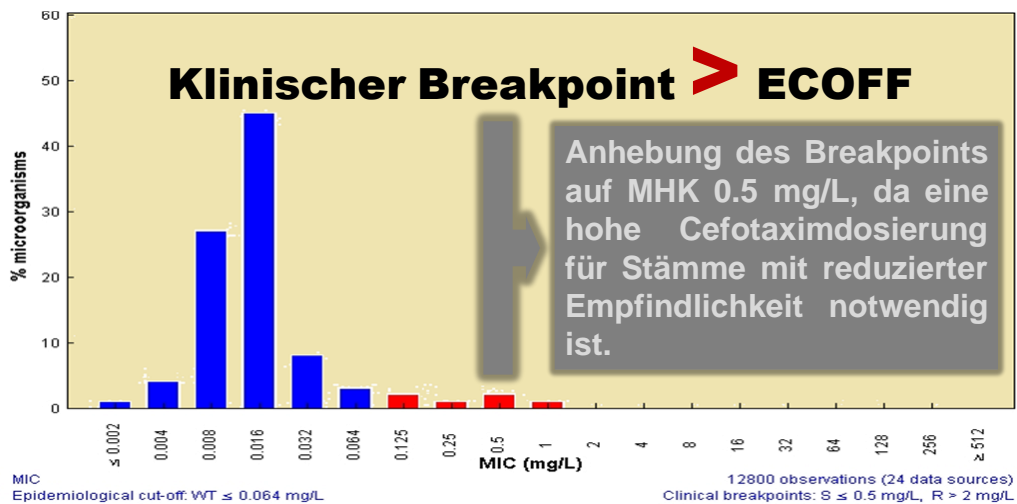
- Der optimale klinische Breakpoint basiert auf
  - ECOFF
  - PK/PD-Grenzwerten
  - klinische Daten



## EUCAST BREAKPOINTS Wo soll der Breakpoint sein?

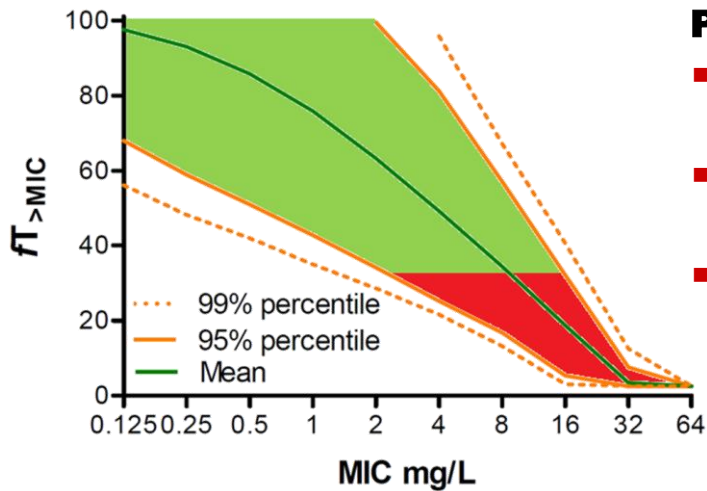


## EUCAST BREAKPOINTS Wildtyp *S. pneumoniae* & Cefotaxim





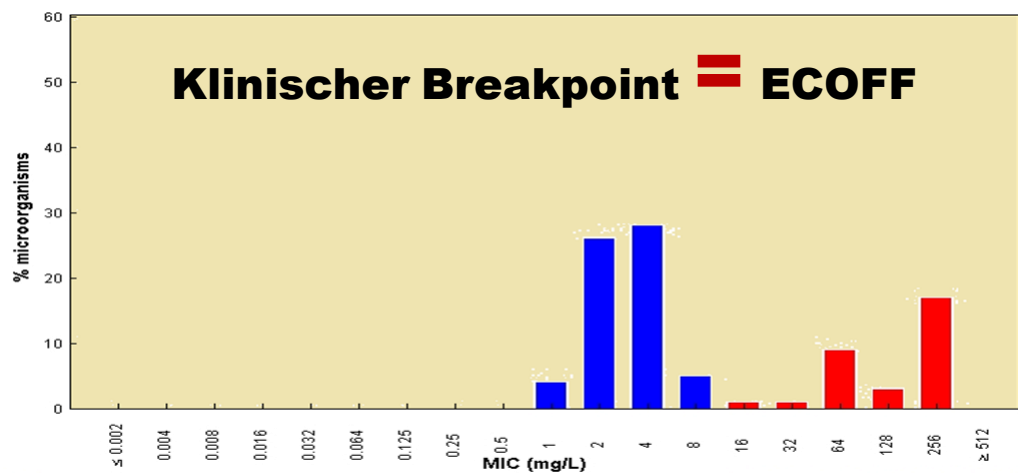
## EUCAST BREAKPOINTS Cefotaxim im klinischen Einsatz



www.eucast.org – Cefotaxim



## EUCAST BREAKPOINTS Wildtyp *E. coli* & Ampicillin



www.eucast.org



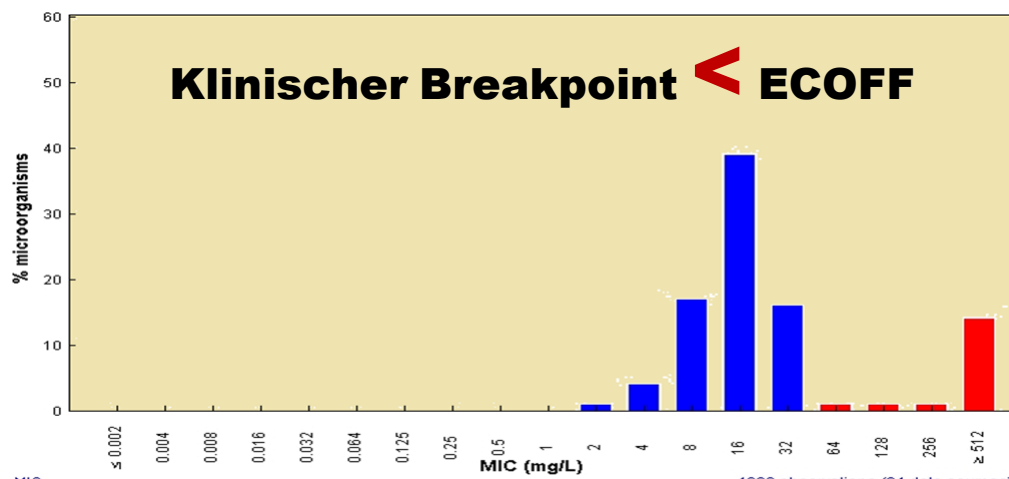
## EUCAST BREAKPOINTS Amoxicillin & PD-abhängige Aktivität

Dosis	3 x 500 mg		3 x 750 mg		4 x 750 mg		3 x 1 g		4 x 1 g		4 x 2 g	
T > MHK (%)	30	40	30	40	30	40	30	40	30	40	30	40
MHK (mg/L)												
0.5	100	100	100	100	100	100	100	100	100	100	100	100
1.0	100	100	100	100	100	100	100	100	100	100	100	100
2.0	100	90	100	99	100	100	100	100	100	100	100	100
4.0	75	20	98	63	100	99	100	90	100	100	100	100
8.0	8	1	39	6	86	39	75	20	99	78	100	100
16.0	0	0	2	0	11	2	8	0	34	8	99	75
32.0	0	0	0	0	0	0	0	0	2	0	34	8

www.eucast.org – Amoxicillin



## EUCAST BREAKPOINTS Wildtyp *E. faecalis* & Gentamicin

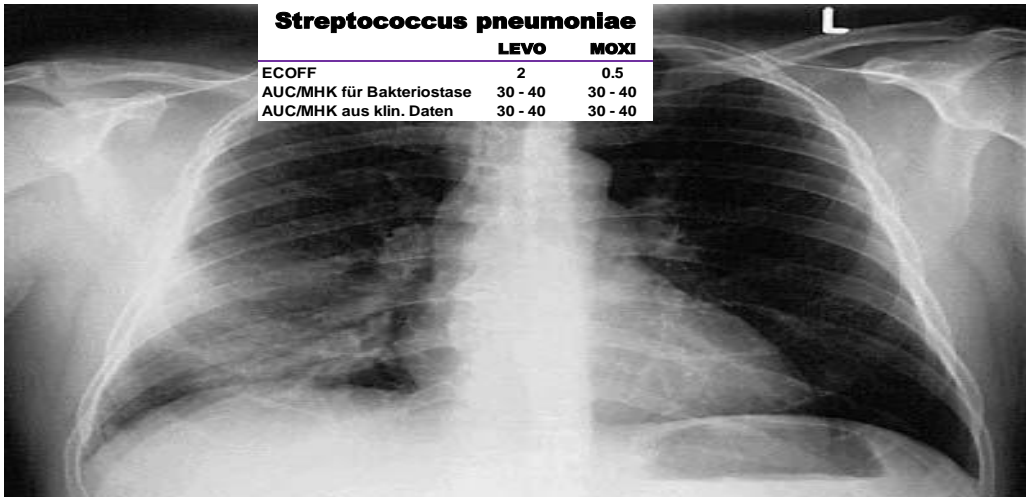


MIC  
Epidemiological cut-off: WT ≤ 32 mg/L

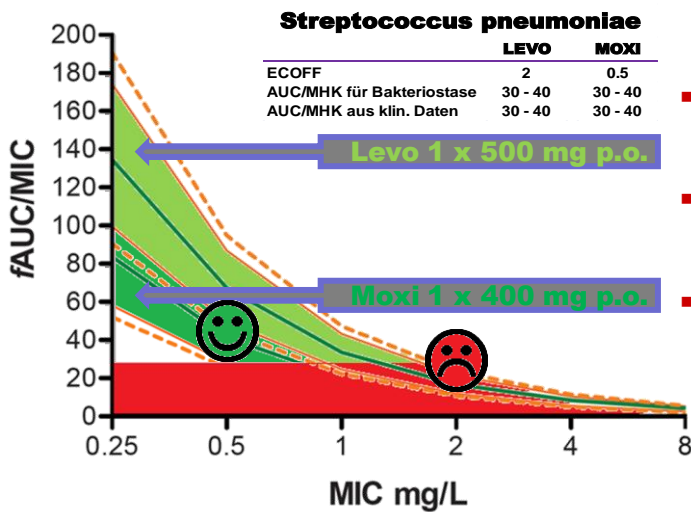
www.eucast.org



## EUCAST BREAKPOINTS Chinolone & Pneumokokken



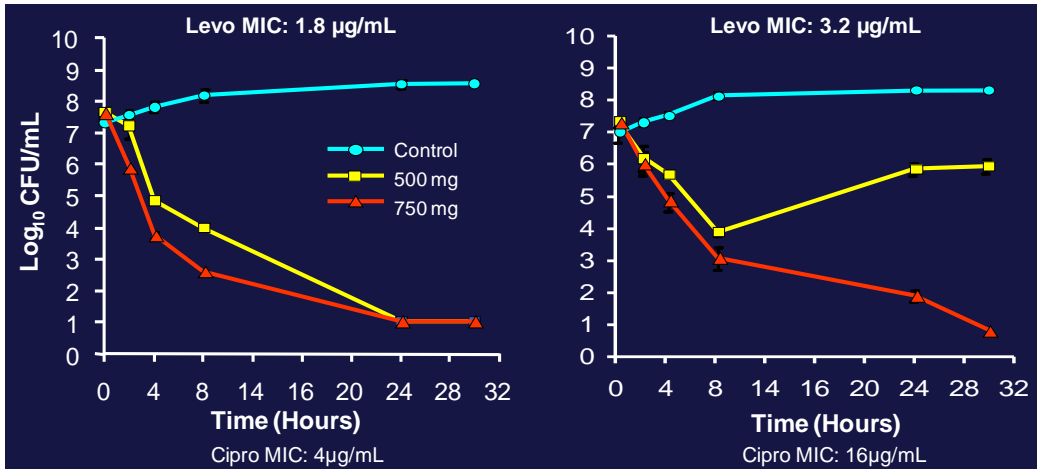
## EUCAST BREAKPOINTS Chinolone & Pneumokokken



- WT *S. pneumoniae* wird als nicht Ciprofloxacin-sensibel angesehen
- WT *S. pneumoniae* wird als nicht Ofloxacin-sensibel angesehen
- Levo-Breakpoints sprechen für die Hochdosistherapie



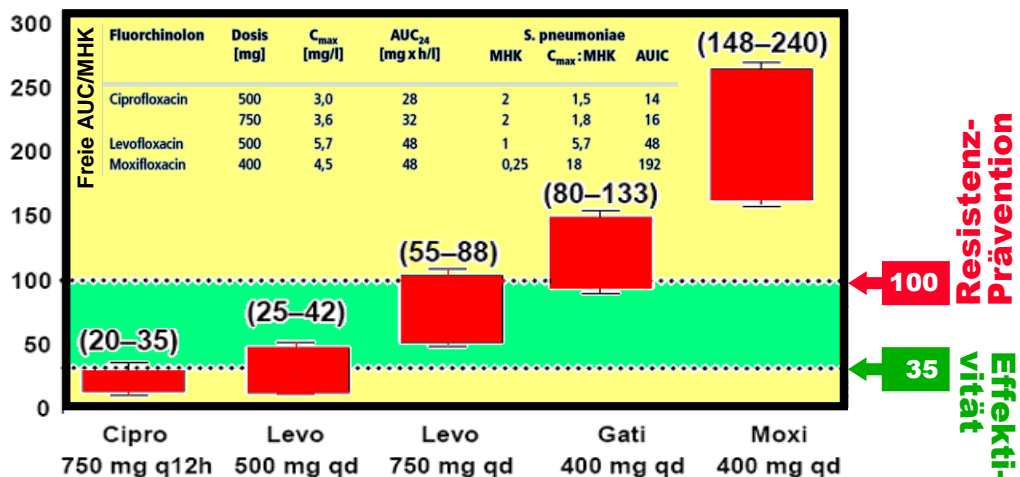
## EUCAST BREAKPOINTS Levofloxacin & Pneumokokken



Lister, Diagn Microbiol Infect Dis 2002



## EUCAST BREAKPOINTS Chinolone & Pneumokokkenpneumonie

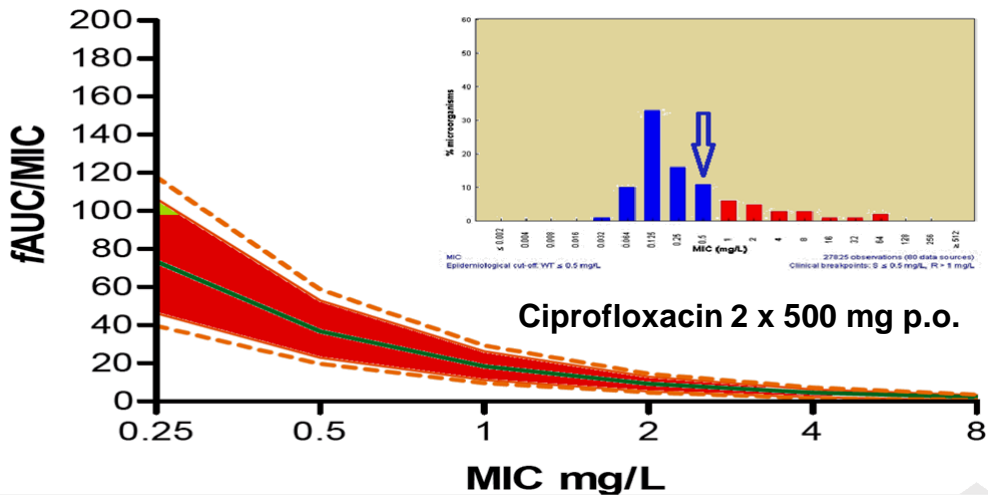


Scheld, Chemother J 2003 – Doern, Clin Infect Dis 2001 – Ball, The Quinolones, 3rd Ed 2000

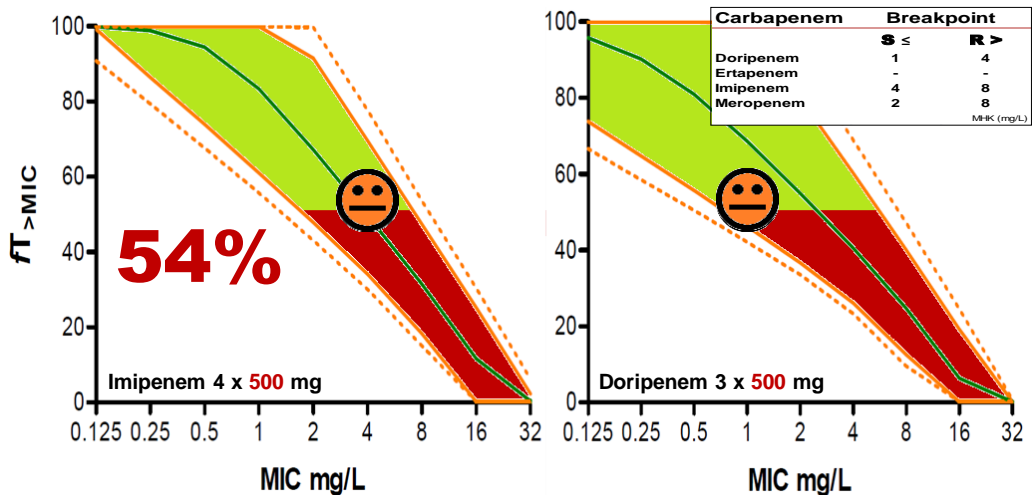




## EUCAST BREAKPOINTS Ciprofloxacin & *P. aeruginosa*

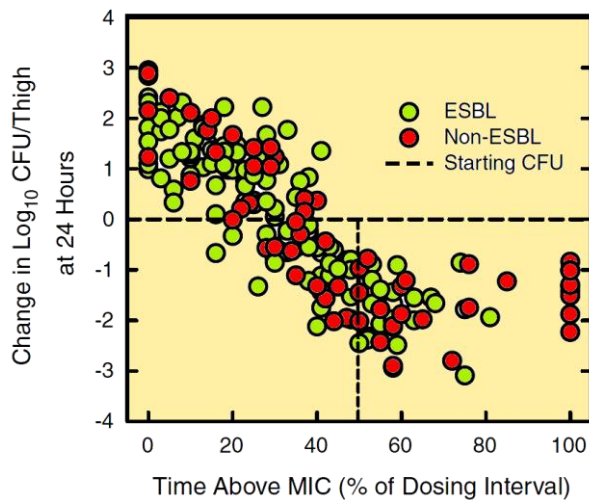


## EUCAST BREAKPOINTS Carbapeneme & *P. aeruginosa*





## EUCAST BREAKPOINTS Betalaktam-AB & ESBL



**ESBL-positive Stämme  
*E. coli* - *K. pneumoniae***

MHK	THERAPIE	
	ERFOLG	VERSAGEN
≤ 1 mg/L	81%	19%
2 mg/L	67%	33%
4 mg/L	27%	73%
8 mg/L	11%	89%

Andes, Clin Microbiol Infect 2005



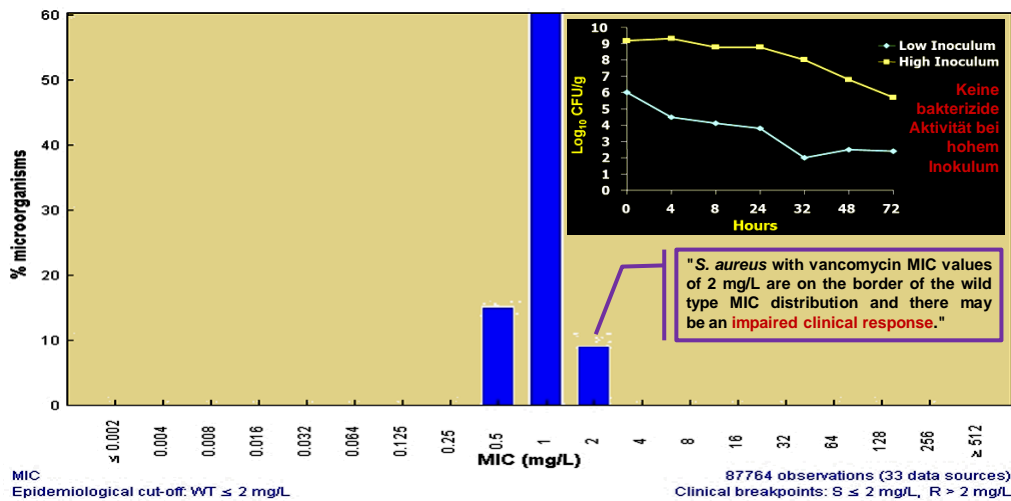
## EUCAST BREAKPOINTS Amoxicillin/Clavulansäure & ESBL

Organisms	Agent	Rule	Scientific basis	Evidence Grade
Enterobacteriaceae (for <i>Klebsiella oxytoca</i> , and <i>Citrobacter koseri</i> see 9.3)	Oxymino cephalosporins, aztreonam	If resistant or intermediate to any 3 <sup>rd</sup> or 4 <sup>th</sup> generation oxymino-cephalosporin or aztreonam, test for ESBL. If positive, report any susceptible results for these cephalosporins (including fourth-generation agents) and for aztreonam as intermediate; and report any intermediate results as resistant. <b>ESBL producers may appear susceptible to penicillin/β-lactamase inhibitor combinations.</b> The use of these combinations against ESBL producers remains controversial, and should be approached with caution.	A few ESBL producers may be tested susceptible in vitro for any of 3 <sup>rd</sup> or 4 <sup>th</sup> generation oxymino-cephalosporin or aztreonam. Efficacy of cefotaxime, ceftazidime and ceftriaxone against ESBL-producing isolates with MICs lower than 2 mg/L remains to be fully documented.	C

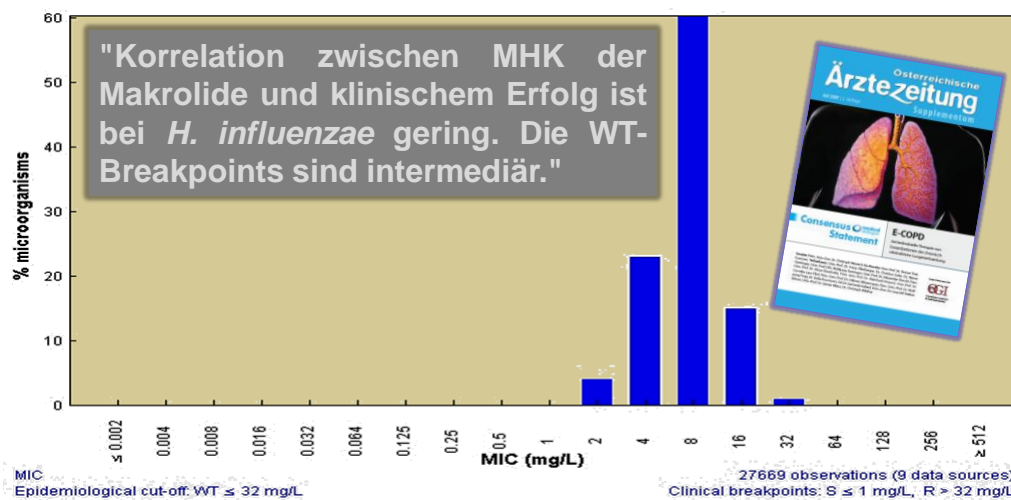
www.eucast.org – Rule 9.1



## EUCAST BREAKPOINTS Vancomycin & *S. aureus*



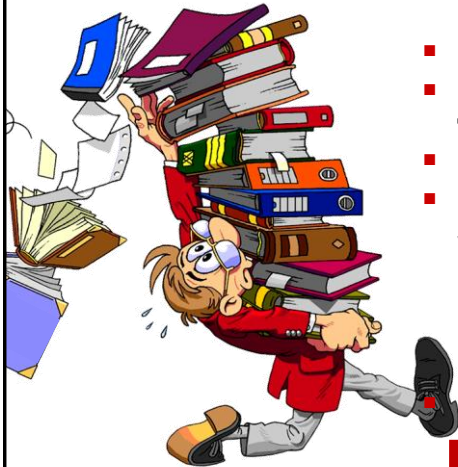
## EUCAST BREAKPOINTS Wildtyp *H. influenzae* & Clarithromycin





# EUCAST BREAKPOINTS

## Zusammenfassung



- **EUCAST ist nicht CLSI**
  - **EUCAST ist datenbezogener und transparenter in der Entscheidung**
  - **EUCAST vereinheitlicht die ABT in EU**
  - **EUCAST ermöglicht aus klinischer Sicht eine rationale ABT, da**
    - **Pharmakokinetik und Pharmakodynamik**
    - **realistische Breakpoints**
    - **klinische Daten**
- berücksichtigt werden  
industriunabhängig**

**EUCAST – yes, we can!**

Univ. Prof. Dr. Florian Thalhammer

## Antibiotika & Antiinfektiva

Rasch nachschlagen – Richtig therapieren



5. erweiterte Auflage

FLORIAN THALHAMMER - MEDIZINISCHE UNIVERSITÄT WIEN - UNIVERSITÄTSKLINIK FÜR INNERE MEDIZIN I - ALLGEMEINES KRANKENHAUS WIEN  
KLINISCHE ABTEILUNG FÜR INFEKTIONEN & TROPENMEDIZIN