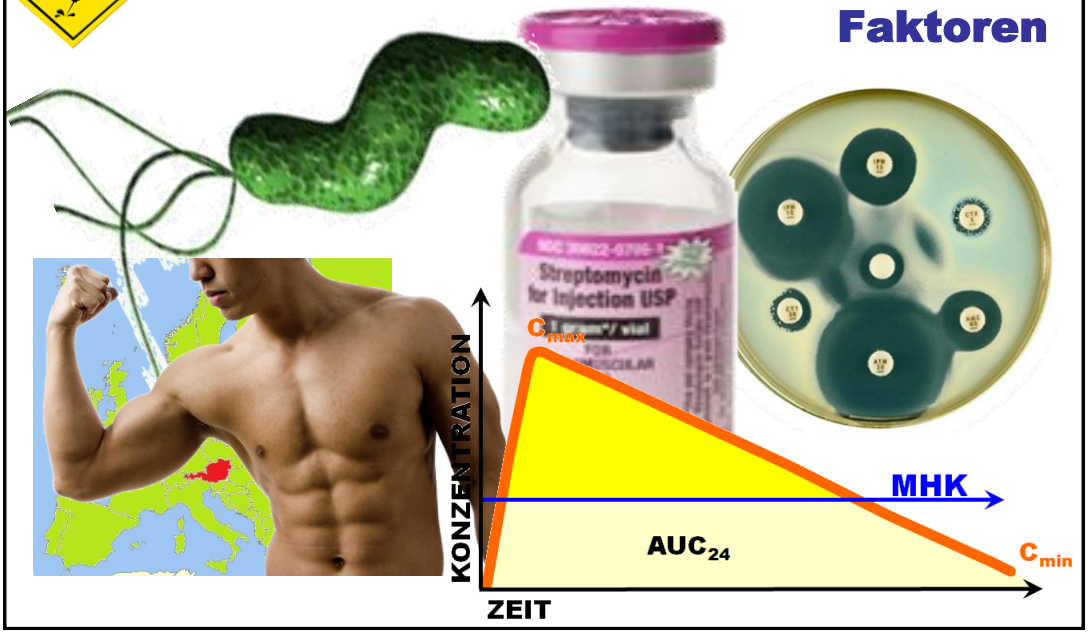
EUCAST BREAKPOINTS
Europa ist anders

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

EUCAST BREAKPOINTS
Faktoren



EUCAST BREAKPOINTS
EUCAST Homepage

www.eucast.org – 12.3.2011

EUCAST BREAKPOINTS
Rational Documents

***Staphylococcus* spp.**

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

Penicillins[1]	MIC breakpoint (mg/L) S ≤	MIC breakpoint (mg/L) R >	Disk content (µg)	Zone diameter breakpoint (mm) S ≥	Zone diameter breakpoint (mm) R <	Notes Numbers for comments on MIC breakpoints Letters for comments on disk diffusion
						1/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[1]	0.125[1,2]	1 unit	26[A,B]	26[A,B]	B. Isolates with inhibition zones above the breakpoint **and** a fuzzy zone edges can be reported susceptible to benzylpenicillin.
Ampicillin	Note[1]	Note[1]	2	15[A,C]	15[A,C]	C. Breakpoints relate to *S. saprophyticus* only.
Ampicillin-sulbactam	Note[1]	Note[1]		Note[A]	Note[A]	
Amoxicillin	Note[1]	Note[1]		Note[A]	Note[A]	
Amoxicillin-clavulanate	Note[1]	Note[1]		Note[A]	Note[A]	
Piperacillin	Note[1]	Note[1]		Note[A]	Note[A]	
Piperacillin-tazobactam	Note[1]	Note[1]		Note[A]	Note[A]	
Ticarcillin	Note[1]	Note[1]		Note[A]	Note[A]	
Ticarcillin-clavulanate	Note[1]	Note[1]		Note[A]	Note[A]	
Phenoxymethylpenicillin	Note[1]	Note[1]		Note[A]	Note[A]	
Oxacillin[2]	Note[1,2]	Note[1,2]		Note[A]	Note[A]	2. *S. aureus* and *S. lugdunensis* with oxacillin MIC values >2 mg/L are mostly methicillin resistant due to the presence of the *mecA* gene. The corresponding oxacillin MIC for coagulase-negative staphylococci is >0.25 mg/L.
Cloxacillin	Note[1]	Note[1]		Note[A]	Note[A]	
Dicloxacillin	Note[1]	Note[1]		Note[A]	Note[A]	
Flucloxacillin	Note[1]	Note[1]		Note[A]	Note[A]	
Mecillinam (uncomplicated UTI only)	-	-		-	-	

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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>	ECOFF≤
Bacteroides fragilis	0	0	0	0	0	0	0	0	0	0	1	19	42	7	0	1	3	2	0	0.25	0.5	ND
Bacteroides fragilis group	0	0	0	0	0	0	0	1	1	11	10	51	91	168	79	105	21	34	19	0.25	0.5	ND
Bacteroides thetaiotaomicron	0	0	0	0	0	0	0	0	0	0	0	0	1	14	1	1	1	7	0	0.25	0.5	ND
Clostridium butyricum	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0.25	0.5	ND
Clostridium difficile	0	0	0	1	1	2	2	56	426	1054	368	264	43	16	5	0	0	0	0	ND	ND	ND
Clostridium perfringens	0	0	0	12	22	23	11	6	2	0	1	0	0	0	0	0	0	0	0	0.25	0.5	0.125
Clostridium ramosum	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0.25	0.5	ND
Clostridium septicum	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0.25	0.5	ND
Clostridium sporogenes	0	0	0	0	1	0	0	3	1	0	0	0	0	0	0	0	0	0	0	0.25	0.5	ND
Clostridium spp	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0.25	0.5	ND
Corynebacterium jeikeium	0	0	0	1	0	1	0	1	1	0	1	3	9	0	1	48	0	0	0	ND	ND	ND
Enterococcus avium	0	0	0	0	0	0	0	1	1	15	28	10	3	2	14	29	0	0	0	ND	ND	ND
Enterococcus casseliflavus	0	0	0	1	0	0	0	0	26	15	8	2	1	1	0	5	0	0	0	ND	ND	ND
Enterococcus faecalis	0	0	0	7	3	3	8	17	68	315	4899	4081	813	227	46	45	0	1	0	ND	ND	16.0
Enterococcus faecium	0	0	0	2	5	7	9	17	27	51	83	157	297	61	120	3026	88	127	42	ND	ND	16.0
	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>	ECOFF≤
Enterococcus gallinarum	0	0	0	0	0	1	0	0	9	32	20	5	3	4	2	26	0	0	0	ND	ND	8.0
Haemophilus influenzae	0	0	0	0	66	106	1198	5555	3528	1359	1195	370	3661	8	32	8	0	13	0	ND	ND	1.0
Haemophilus parainfluenzae	0	0	0	0	7	6	8	5	20	25	21	12	25	0	0	0	0	0	0	ND	ND	ND
Listeria monocytogenes	0	0	0	7	1	5	13	82	136	28	1	0	0	0	0	0	0	0	0	ND	ND	1.0
Neisseria gonorrhoeae	0	1	104	465	183	620	1818	1520	778	1023	365	76	46	424	2	1	0	0	0	0.064	1.0	ND
Neisseria meningitidis	0	4	11	154	770	1677	683	367	116	23	1	0	0	0	0	0	0	0	0	0.064	0.25	0.25
Peptostreptococcus spp	0	1	0	3	2	2	5	3	0	0	0	0	0	0	0	0	0	0	0	0.25	0.5	ND

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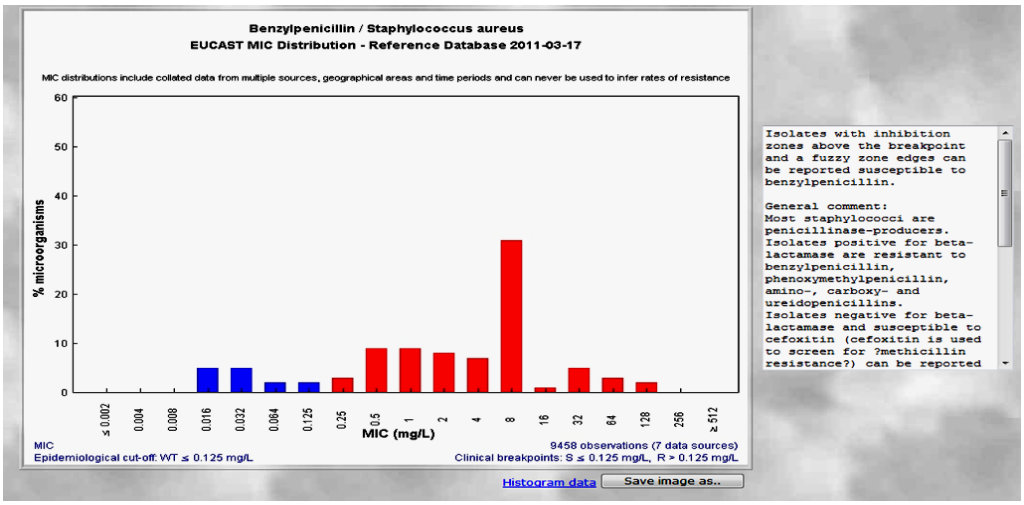
EUCAST BREAKPOINTS
Rational Documents



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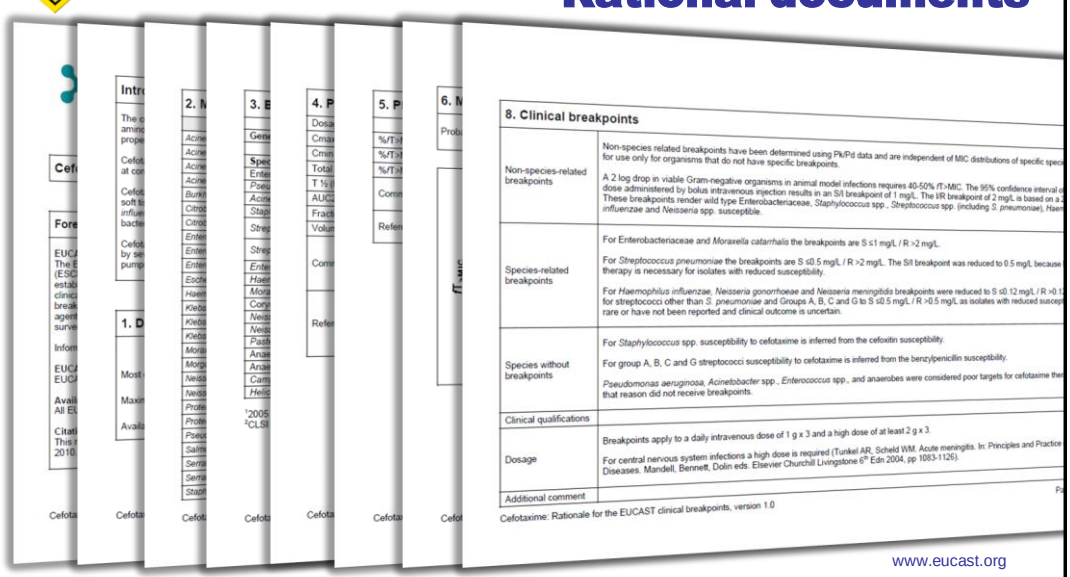
EUCAST BREAKPOINTS
Rational documents



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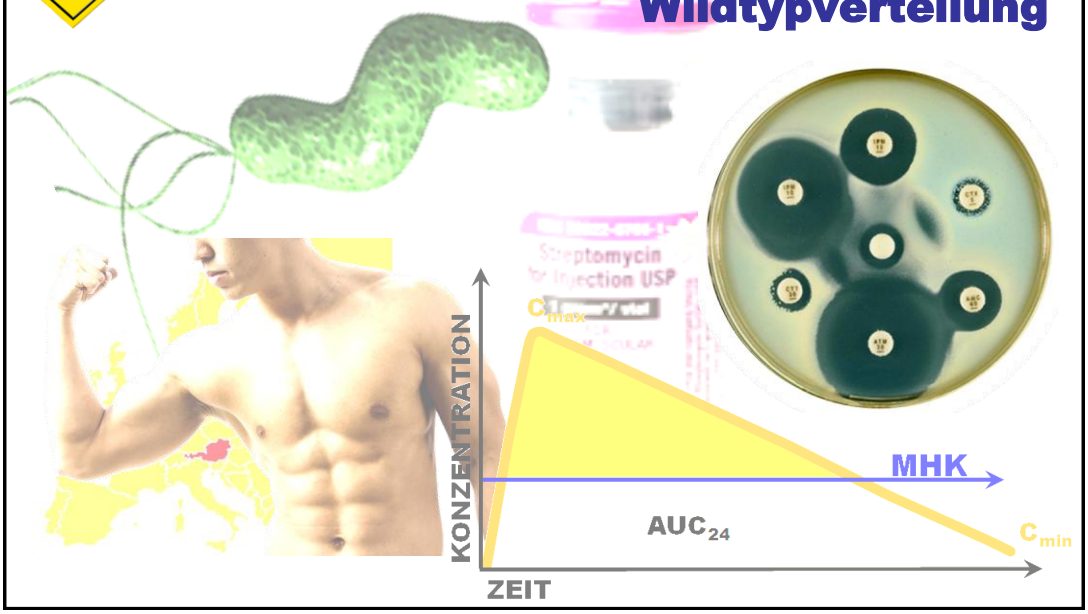
EUCAST BREAKPOINTS
Wildtypverteilung



EUCAST BREAKPOINTS
Historische Breakpoints

Cefotaxim bei *Escherichia coli*

		S	R
BSAC	Großbritannien	≤ 2	≥ 4
CA-SFM	Frankreich	≤ 4	> 32
CRG	Holland	≤ 4	> 16
DIN	Deutschland	≤ 2	≥ 16
NWGA	Norwegen	≤ 1	≥ 32
SRGA	Schweden	≤ 0.5	≥ 2

EUCAST BREAKPOINTS
Wildtyp Definition

- Als WT eines Erregers wird jener Stamm bezeichnet, der
  - ohne erworbene Resistenz oder
  - durch Mutation entstandene Resistenz

  gegen 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.

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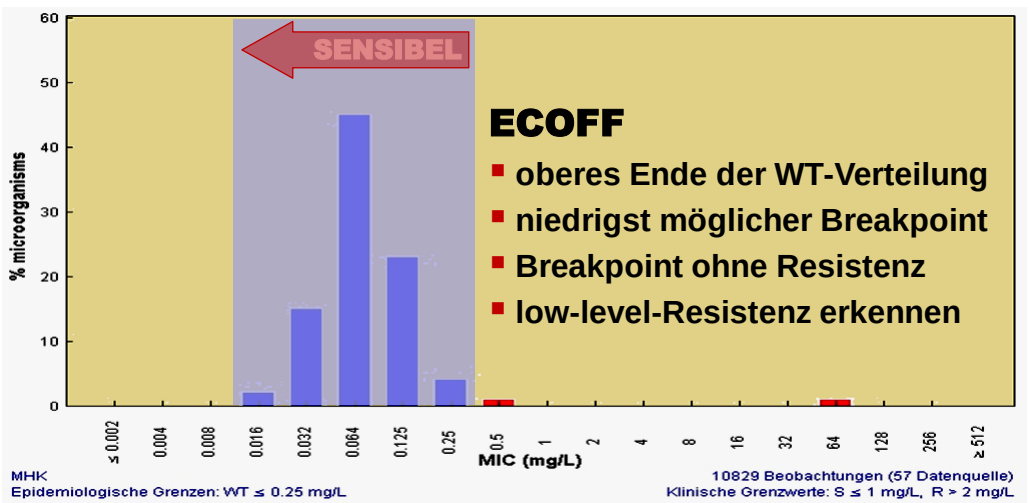
EUCAST BREAKPOINTS
Wildtyp *E. coli* & Cefotaxim



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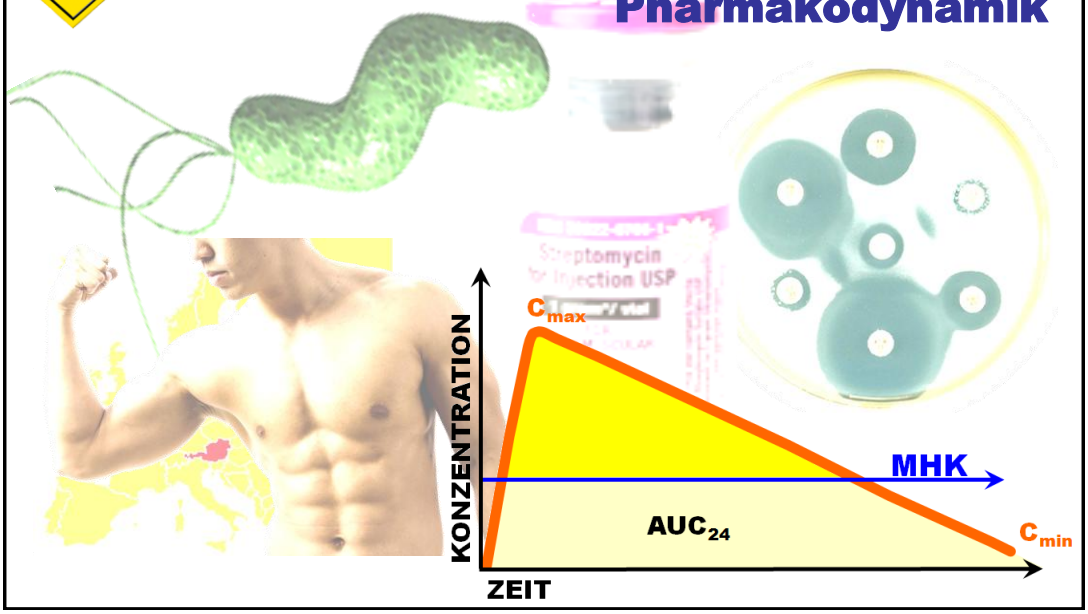
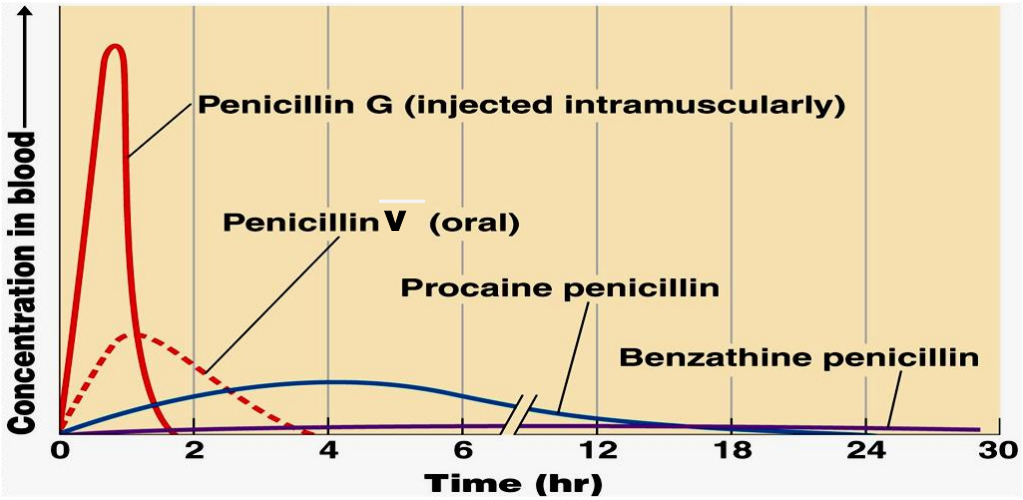
EUCAST BREAKPOINTS
MHK oberhalb des ECOFF

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

EUCAST BREAKPOINTS
Pharmakodynamik



EUCAST BREAKPOINTS
Pharmakologie



EUCAST BREAKPOINTS
Pharmakodynamische Therapieprinzipien

KONZENTRATION (C_{max})

- **Spitzenspiegel/MHK**
  - > Aminoglykoside, Azithromycin
  - > Chinolone, Metronidazol, Daptomycin
- **AUC_{24}/MHK**
  - > Fluorochinolone, Tigecyclin
  - > Vancomycin, Daptomycin
- **Zeit oberhalb der MHK**
  - > Penicilline, Cephalosporine
  - > Carbapeneme, Aztreonam, Linezolid
  - > Makrolide, Clindamycin

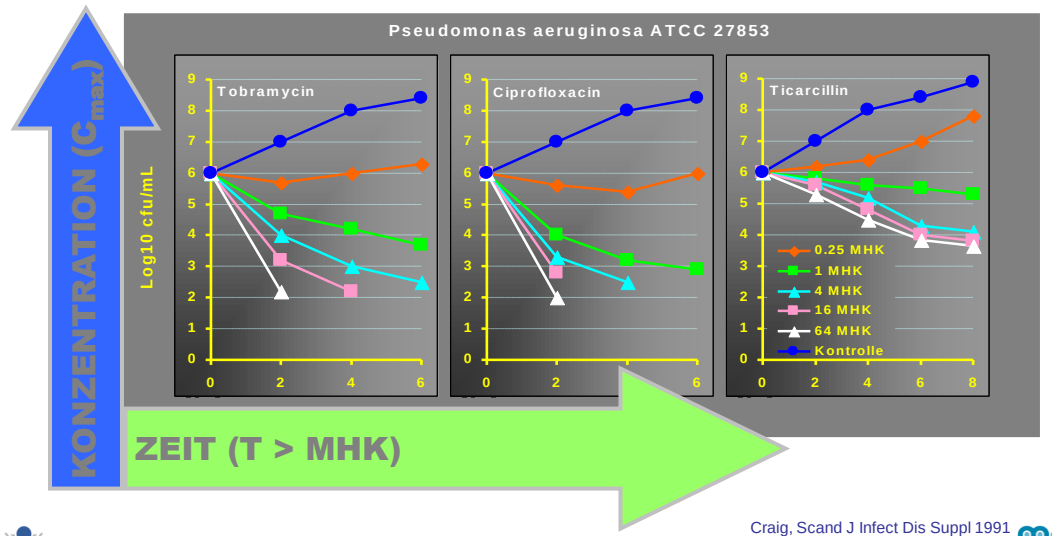
ZEIT (T > MHK)

FLÄCHE (AUC_{24}/MHK)

KONZ
je höher, desto besser

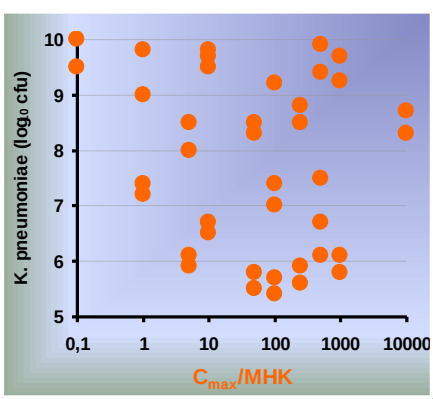
ZEIT
je länger, desto besser

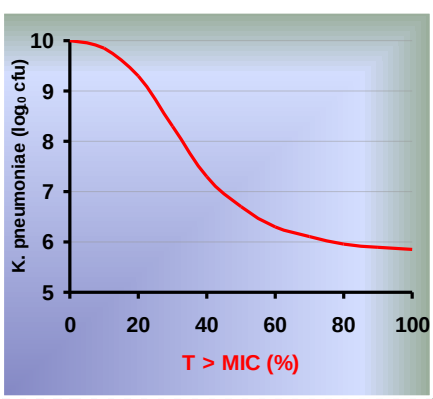
EUCAST BREAKPOINTS
Pharmakodynamik im Überblick



Craig, Scand J Infect Dis Suppl 1991

EUCAST BREAKPOINTS
Zeit vs Konzentration

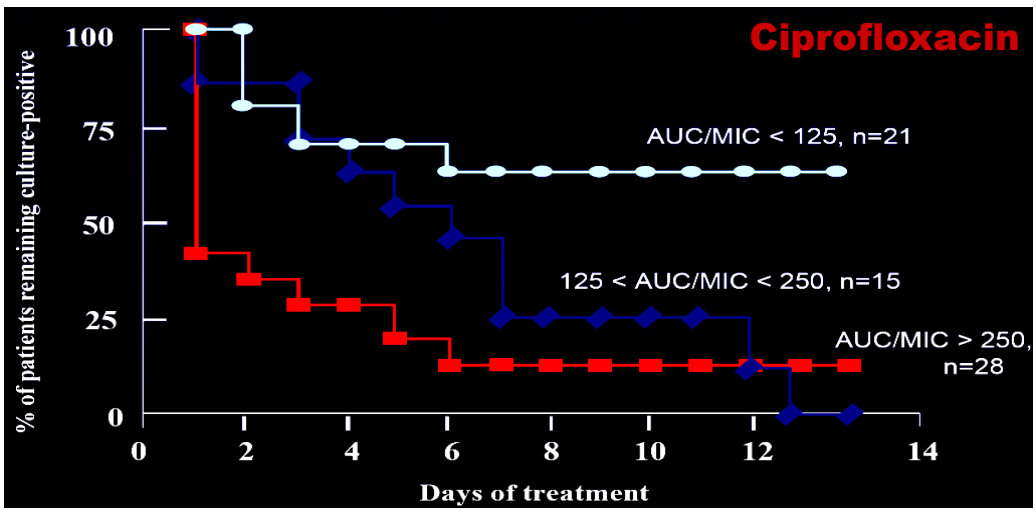




BETALAKTAM-ANTIBIOTIKA

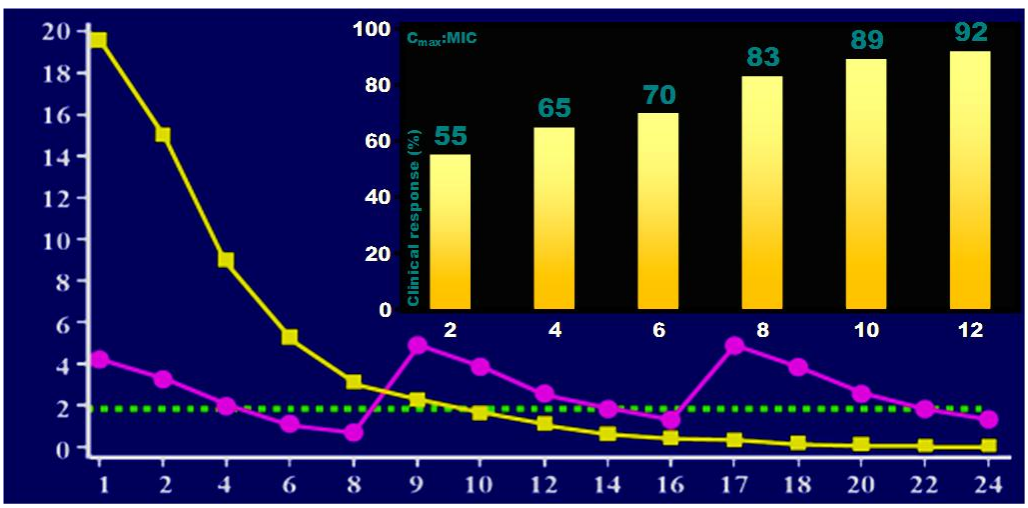
Craig , Diagn Microbiol Infect Dis 1995

EUCAST BREAKPOINTS
AUC vs MHK



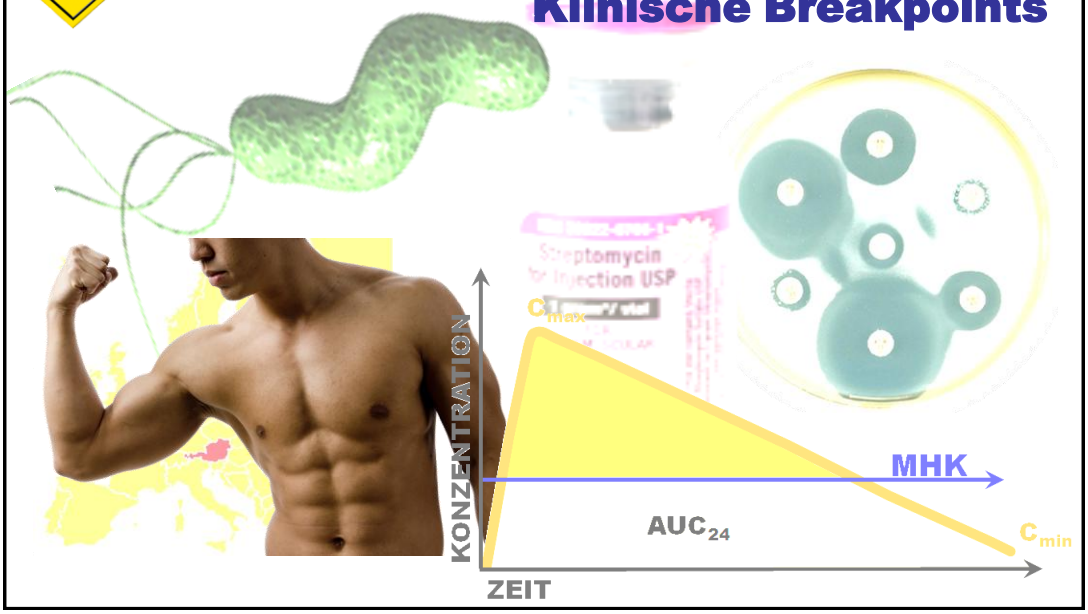
Forrest, Antimicrob Agents Chemother 1993

EUCAST BREAKPOINTS
Cmax vs MHK



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

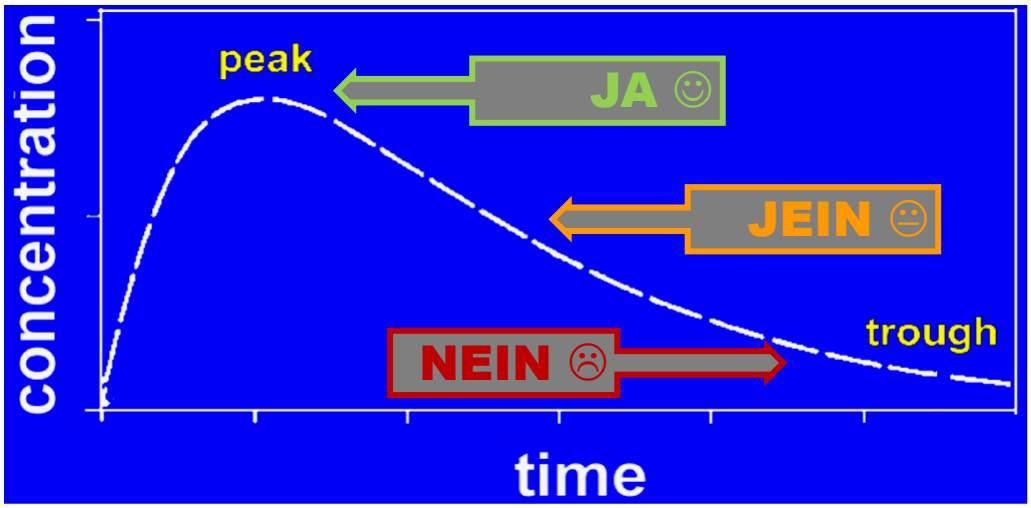
EUCAST BREAKPOINTS
Klinische Breakpoints



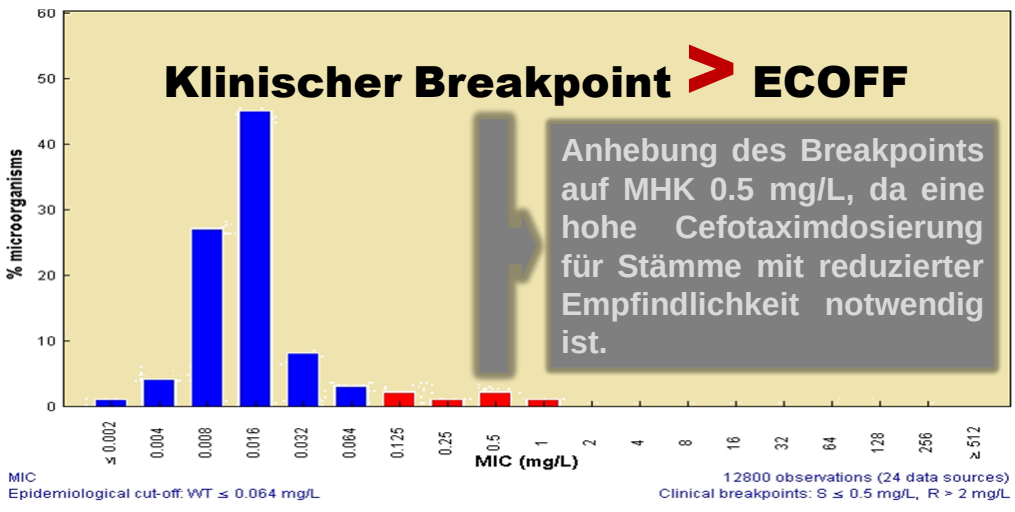
EUCAST BREAKPOINTS
Bestimmung des klinischen Breakpoints

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

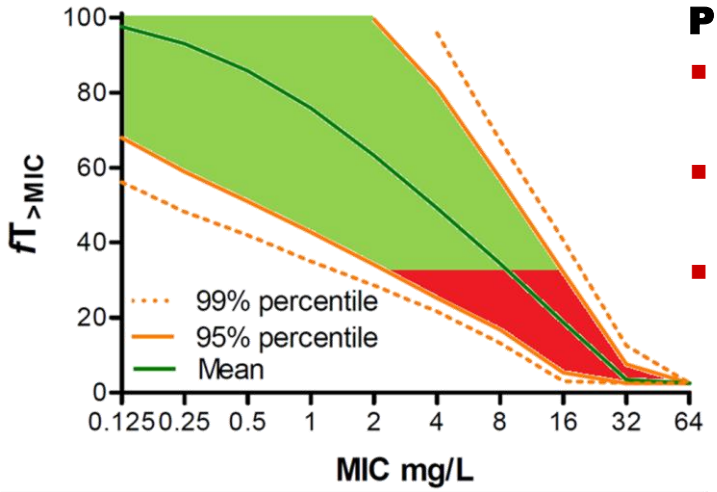
EUCAST BREAKPOINTS
Wo soll der Breakpoint sein?



EUCAST BREAKPOINTS
Wildtyp *S. pneumoniae* & Cefotaxim



EUCAST BREAKPOINTS
Cefotaxim im klinischen Einsatz

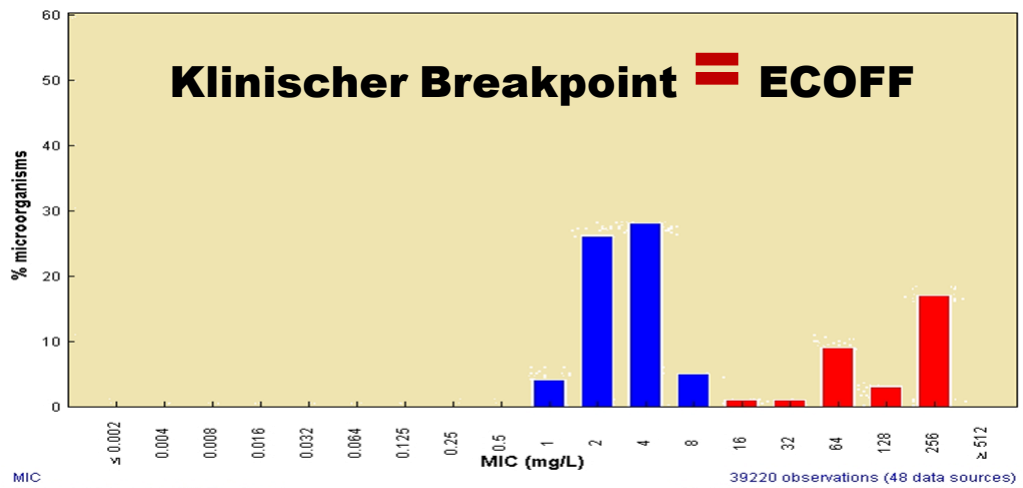


PD-Kenngrößen

- Enterobakterien
  - 36 – 40
- Pneumokokken
  - 36 – 40
- *S. aureus*
  - 20 – 28

www.eucast.org – Cefotaxim

EUCAST BREAKPOINTS
Wildtyp *E. coli* & Ampicillin



MIC
Epidemiological cut-off: WT ≤ 8 mg/L

39220 observations (48 data sources)
Clinical breakpoints: S ≤ 8 mg/L, R > 8 mg/L

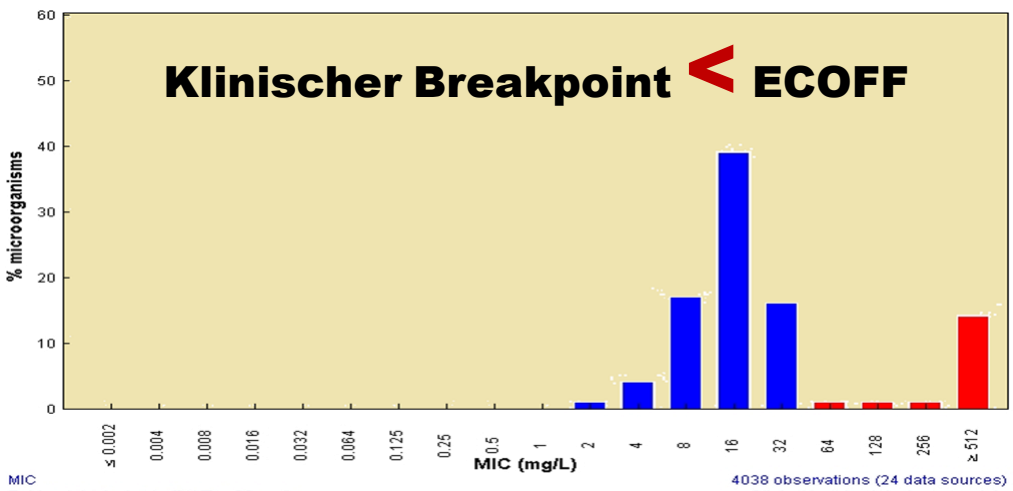
www.eucast.org

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								
1.0	100	100	100	100	100	100	100	100				
2.0	100	90	100	99	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

4038 observations (24 data sources)
Clinical breakpoints: Inappropriate

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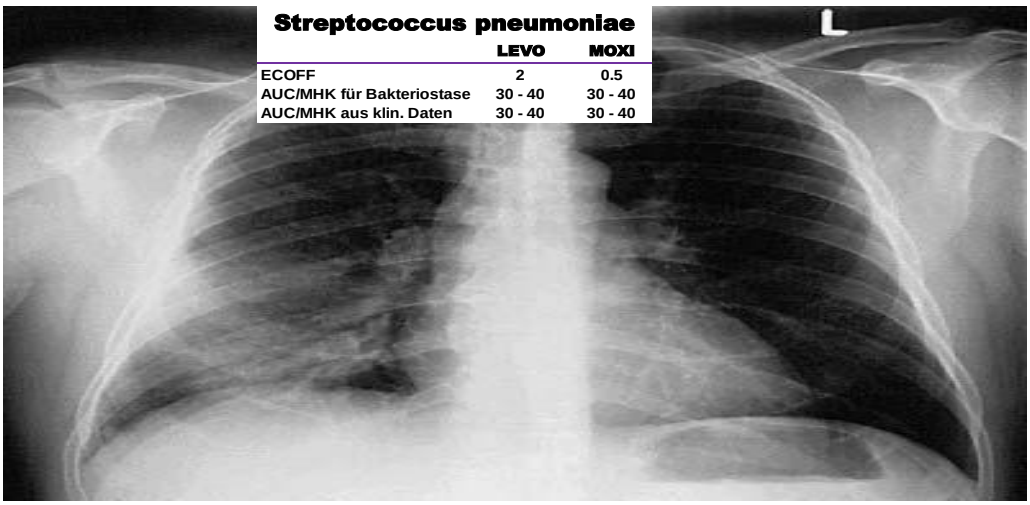
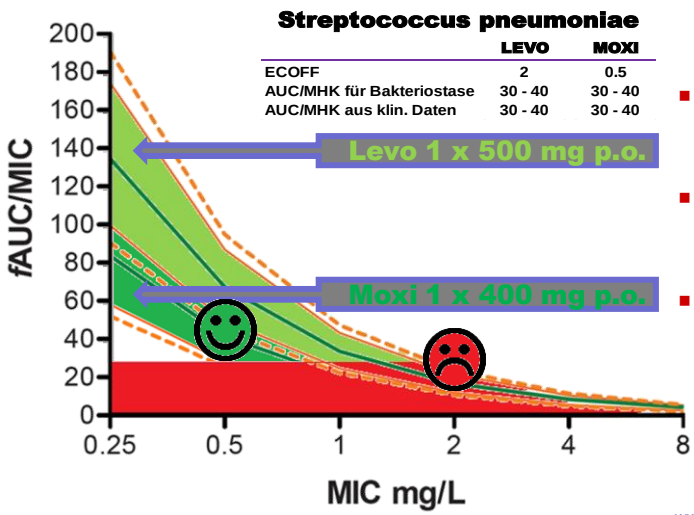
EUCAST BREAKPOINTS
Chinolone & Pneumokokken



Streptococcus pneumoniae

	LEVO	MOXI
ECOFF	2	0.5
AUC/MHK für Bakteriostase	30 - 40	30 - 40
AUC/MHK aus klin. Daten	30 - 40	30 - 40

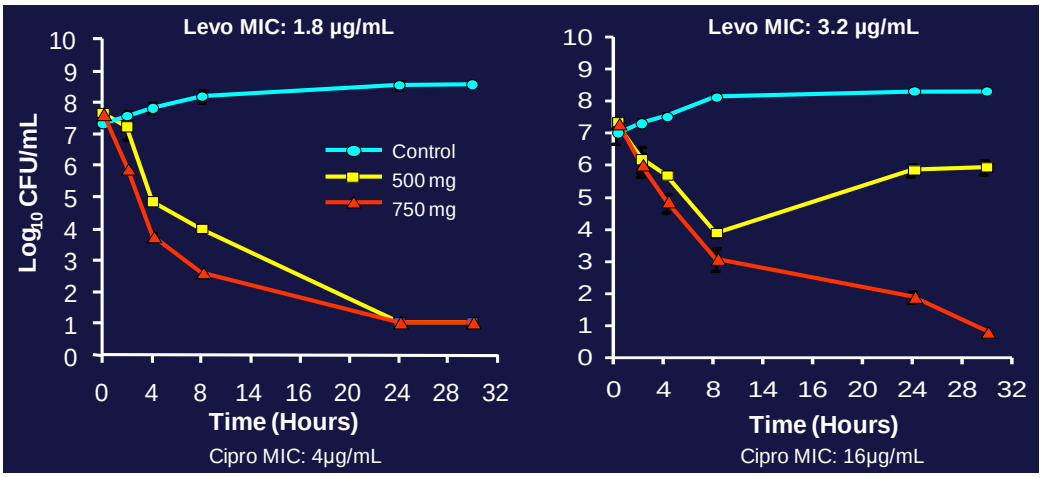
EUCAST BREAKPOINTS
Chinolone & Pneumokokken



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

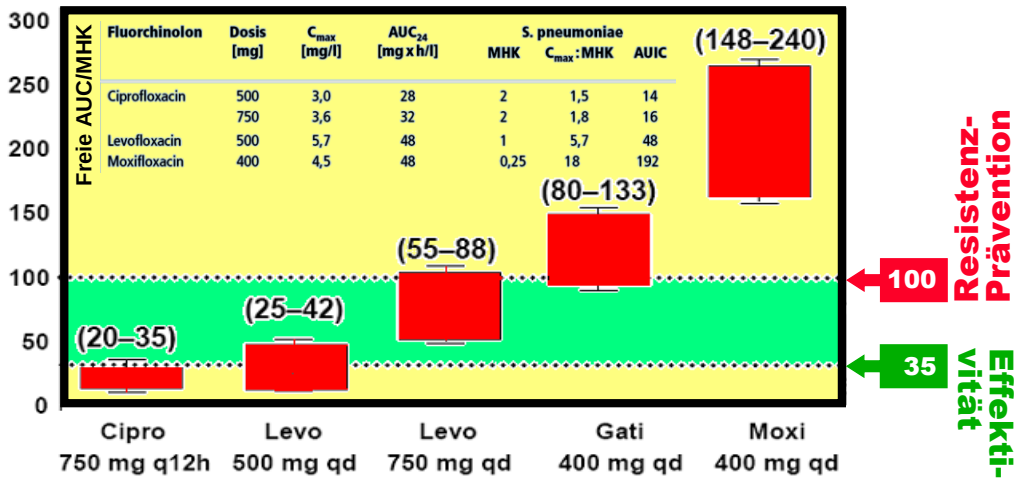
www.eucast.org – Levofloxacin & Moxifloxacin

EUCAST BREAKPOINTS
Levofloxacin & Pneumokokken



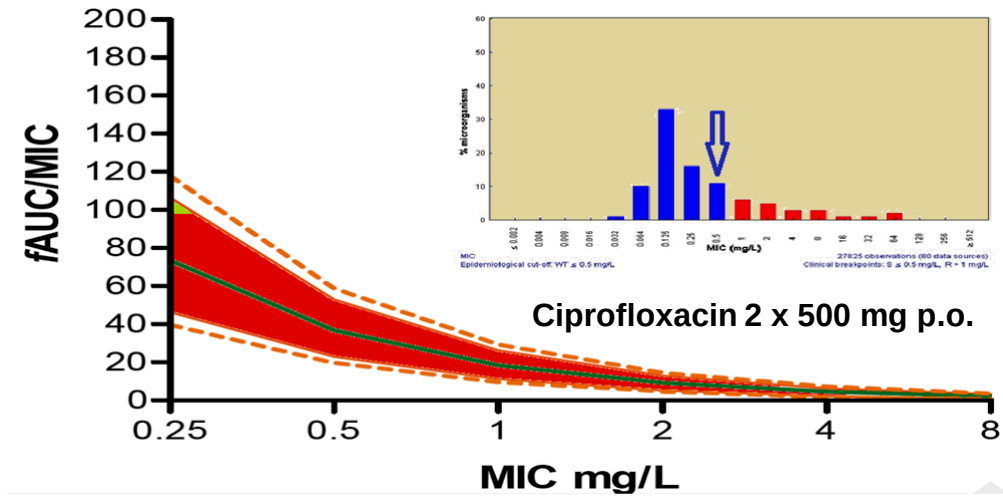
Lister, Diagn Microbiol Infect Dis 2002

EUCAST BREAKPOINTS
Chinolone & Pneumokokkenpneumonie



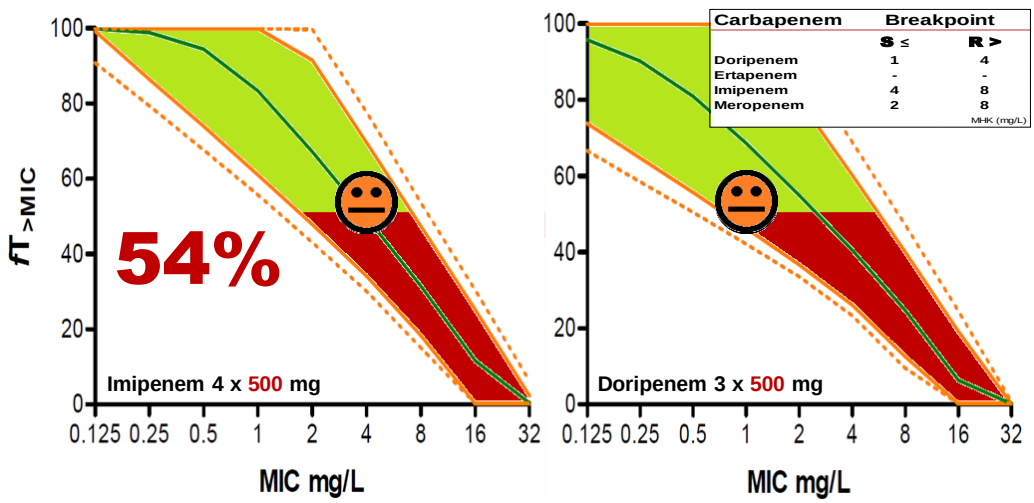
Scheld, Chemother J 2003 – Doern, Clin Infect Dis 2001 – Ball, The Quinolones, 3rd Ed 2000

EUCAST BREAKPOINTS
Ciprofloxacin & *P. aeruginosa*



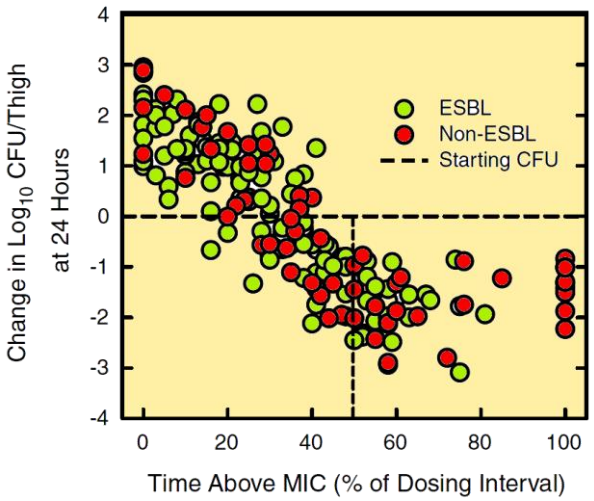
www.eucast.org – Ciprofloxacin

EUCAST BREAKPOINTS
Carbapeneme & *P. aeruginosa*



www.eucast.org – Doripenem & Imipenem

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%

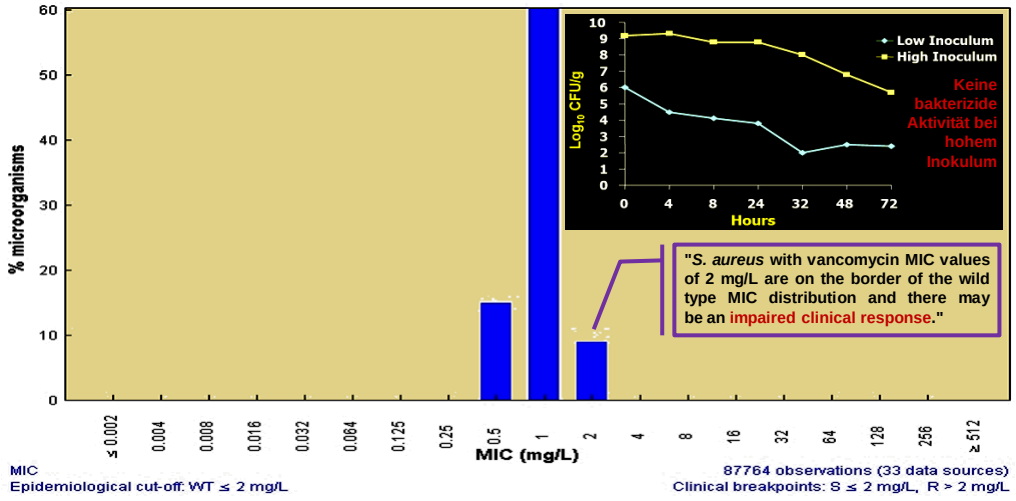
Andes, Clin Microbiol Infect 2005

EUCAST BREAKPOINTS
Amoxicillin/Clavulansäure & ESBL

Organisms	Agent	Rule	Scientific basis	Evidence Grade
Enterobacteriaceae (for *Klebsiella oxytoca*, and *Citrobacter koseri* see 9.3)	Oxyimino cephalosporins, aztreonam	If resistant or intermediate to any 3rd or 4th generation oxyimino-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. ESBL producers may appear susceptible to penicillin/β-lactamase inhibitor combinations. 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 3rd or 4th generation oxyimino-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*

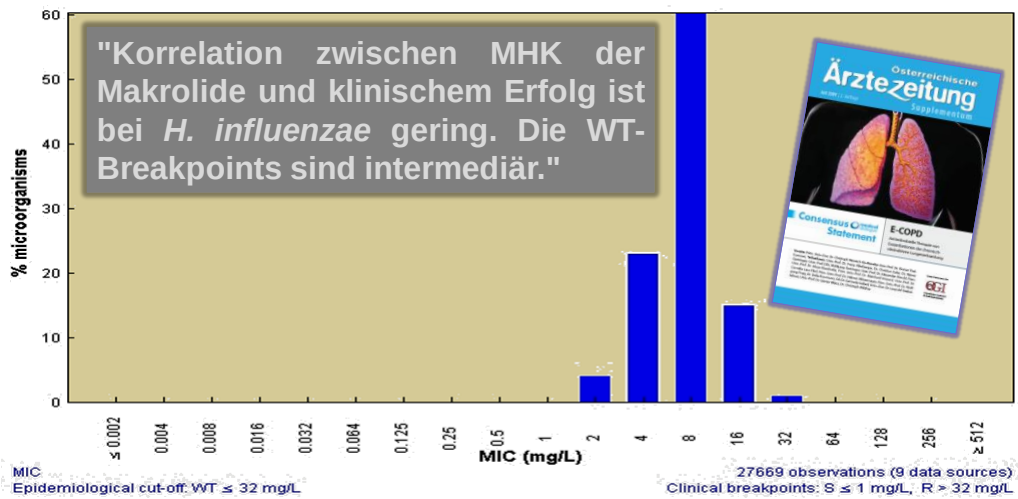


MIC
Epidemiological cut-off: WT ≤ 2 mg/L

87764 observations (33 data sources)
Clinical breakpoints: S ≤ 2 mg/L, R > 2 mg/L

www.eucast.org - Vancomycin

EUCAST BREAKPOINTS
Wildtyp *H. influenzae* & Clarithromycin

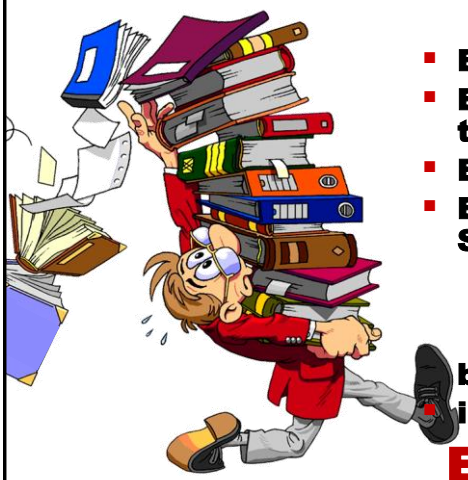


MIC
Epidemiological cut-off: WT ≤ 32 mg/L

27669 observations (9 data sources)
Clinical breakpoints: S ≤ 1 mg/L, R > 32 mg/L

www.wucast.org – Clarithromycin

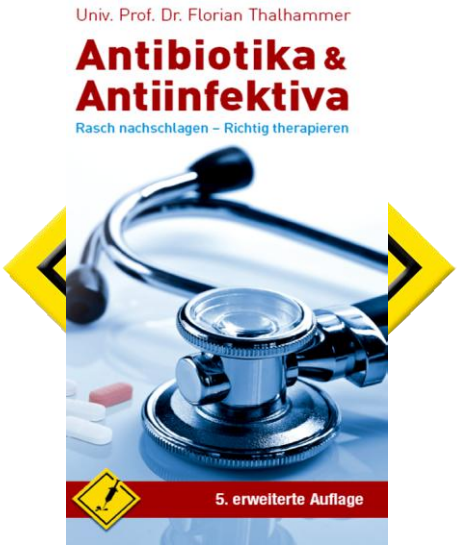
EUCAST BREAKPOINTS
Zusammenfassung



- **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
- **industrieunabhängig**

EUCAST – yes, we can!



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KLINISCHE ABTEILUNG FÜR INFEKTIONEN & TROPENMEDIZIN