Die Entwicklung von EUCAST

B. Wiedemann

Standardisierung der Empfindlichkeits-prüfungen durch Fachgremien

- DIN (D)
- NCCLS CLSI(USA)
- Stokes Method
- BSAC (GB)
- CA-SFM (F)
- Mensura (E)
- SRGA (S)
- ....
- EUCAST
- CEN

Agardiffusionsteste

- **Antibiotic susceptibility testing by a standardized single disk method.**
  - Bauer AW, Kirby WM, Sherris JC, Turck M
  - Am J Clin Pathol. 1966 Apr;45(4):493-6.
- **Antibiotic sensitivity testing. Report of an international collaborative study**
  - Ericsson HM, Sherris JC.
  - Acta Pathol Microbiol Scand B Microbiol Immunol. 1971;217:Suppl 217:1+.

DIN
Deutsches Institut für Normung

- Normenausschuss Medizin (NAMed)
- Fachbereich E Medizinische Mikrobiologie und Immunologie
  - AA E 10 Chemotherapeutische Untersuchungsmethoden (Anfang der 1970er Jahre)
  - Vorsitz: Linzenmeyer
  - Mitglieder:
    - Knothe
    - Naumann
    - Ritzerdfeld
    - Industrievertreter
    - ...uvam

Aufgaben im Normenausschuss

- Festlegung der Methode
  - Agardiffusion (Ericson & Sherris)
    - Medium
    - Testblättchen
    - Inoculum
  - MHK-Bestimmung
    - Medium
    - Inoculum
    - Makro – Mikro
- Bewertung der Ergebnisse

Korrelation zwischen beiden Methoden

Grundlagen zur Beurteilung der Wirksamkeit

1950 Eagle et al Bakterizidie Level (T>MHK)
1953 Dost Pharmakokinetik
1956 Rodger et al. Def.:Resistenz - Dosierungen
1956 Goodman 2 – 5 x MHK = Serumkonzentration
1973 Rules and Regulations: antibiotic susceptiility discs. FDA
1973 erste DIN-Norm

- Jedes europäische Land fertigte seine eigene Norm
- In den USA: NCCLS

Grundlagen zur Beurteilung der Wirksamkeit 2

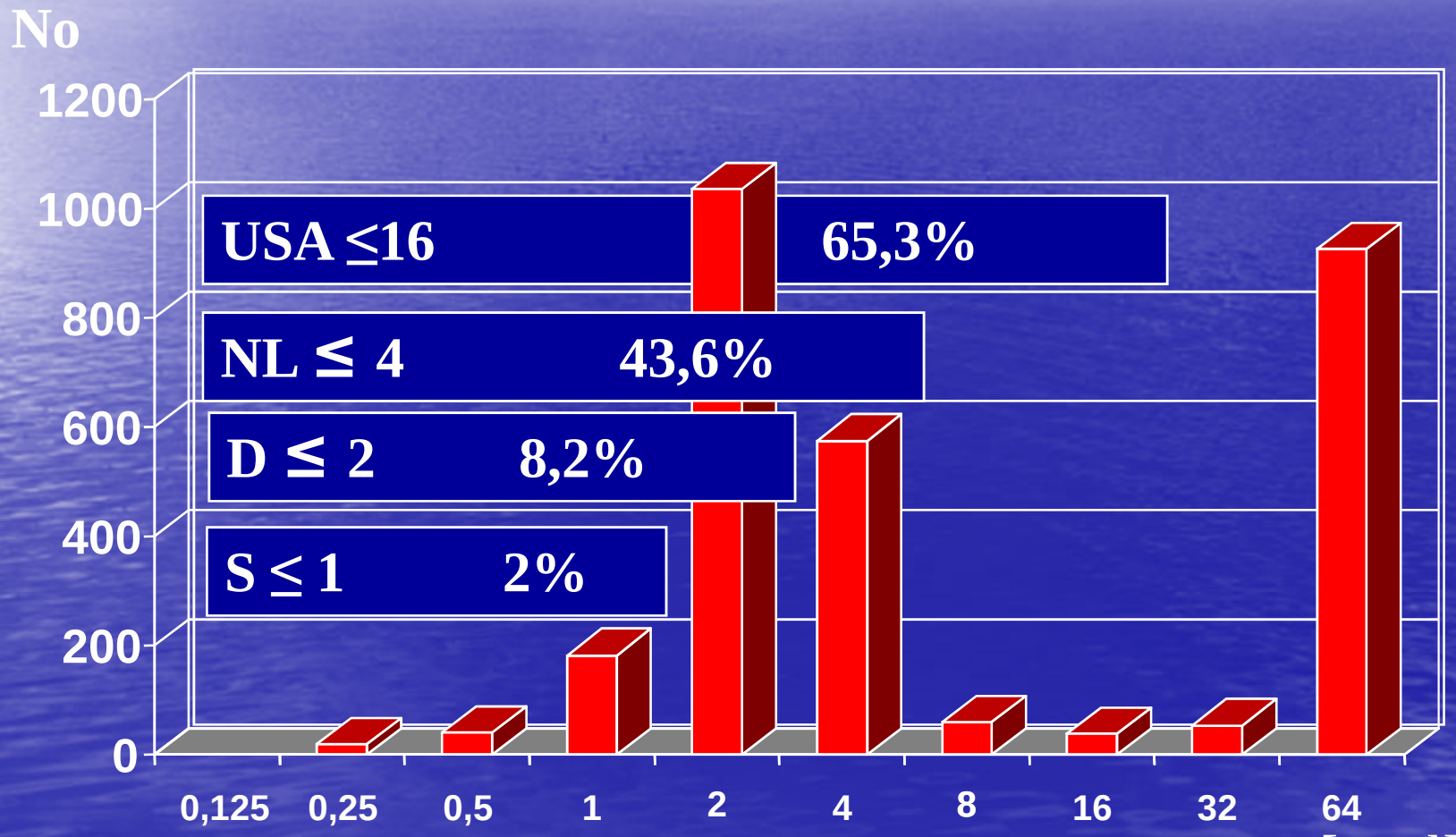
1971 Naumann t/2 (MHK ≤ C in der Mitte der Applikation)

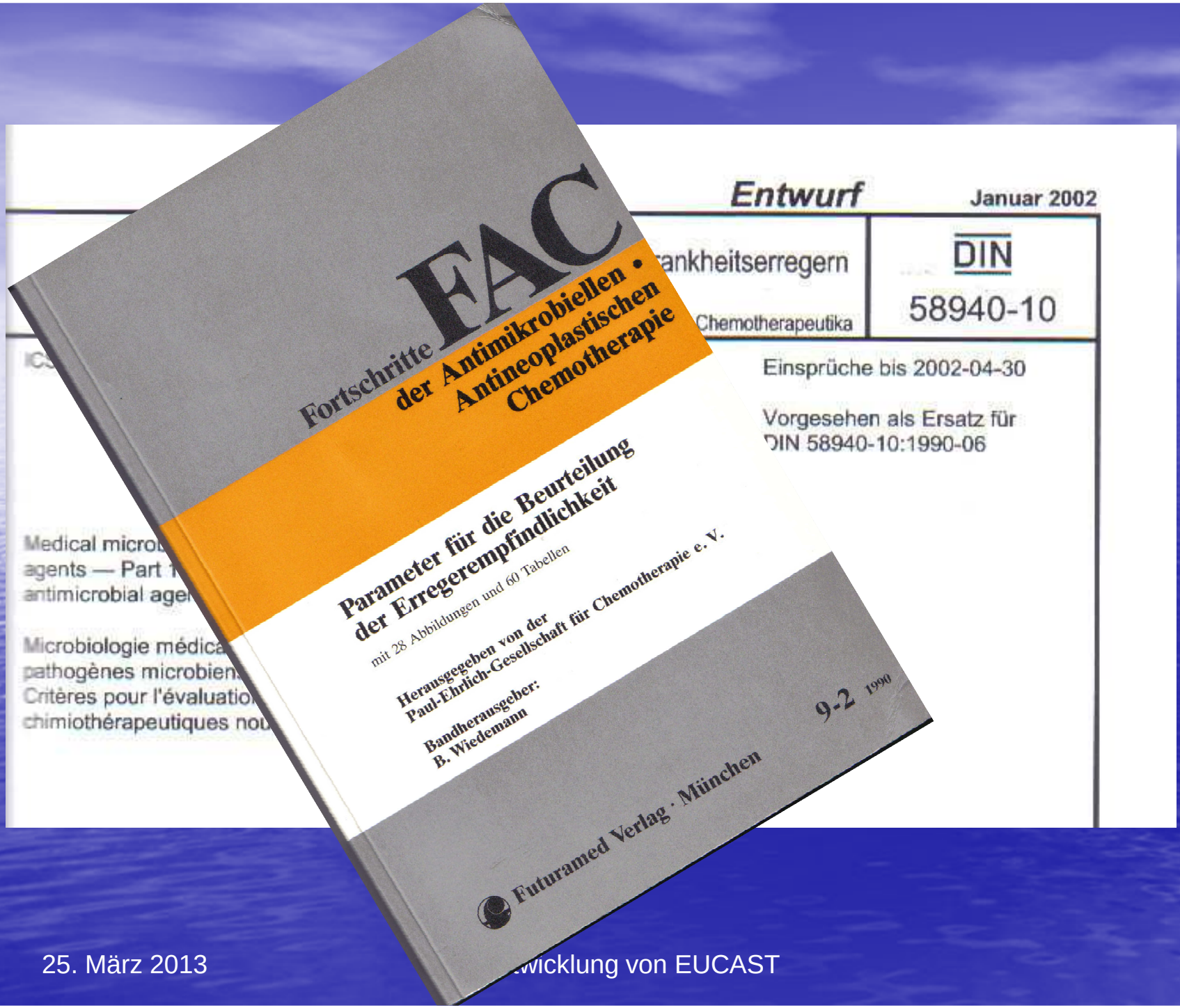
1974 Klastersky et al Peaktiter im Serum 1:8

1980 Ellner u Neu IQ = C_{max}/MHK

MHK-Verteilung: Ampicillin - E.coli

Grenzwert und % empfindliche Stämme




Entwurf
Januar 2002
ankheitserregern
Chemotherapeutika
DIN
58940-10
Einsprüche bis 2002-04-30
Vorgesehen als Ersatz für
DIN 58940-10:1990-06
Medical microb
agents — Part 1
antimicrobial age
Microbiologie médica
pathogènes microbien
Critères pour l'évaluatio
chimiothérapeutiques nou
Fortschritte
FAC
der Antimikrobiellen •
Antineoplastischen
Chemotherapie
Parameter für die Beurteilung
der Erregerempfindlichkeit
mit 28 Abbildungen und 60 Tabellen
Herausgegeben von der
Paul-Ehrlich-Gesellschaft für Chemotherapie e. V.
Bandherausgeber:
B. Wiedemann
9-2 1990
Futuramed Verlag · München

EUCAST
Komitee der ESCMID

EU**R**opean
Committee on
Antimicrobial
Susceptibility
Testing

Gegründet 1997
Neu gestaltet 2002
Finanziert durch:
- ESCMID
- Nationale Komitees
- Europäische Union

EUCAST 1997 - 2002

Ian Phillips (Vorsitz)
Tom Bergan (Schriftführer)
1 Vertreter aus jedem Europäischen Land

Beispielsweise:

Acar
Baquero
Cars
Wiedemann
Mittermaier
ua

neue Antibiotika, Methode, Bewertung

EUCAST 2002

Gunnar Kahlmeter

Harmonisierung aller Grenzwerte, Methoden und Interpretationen in Europa

Neue Regeln

EUCAST

- General Committee
- Steering Committee
  - Vorsitzende der nationalen Gremien für Deutschland Arne Rodlof (DIN)
- EUCAST industry email network

www.eucast.org

Ziele von EUCAST

- Netzwerk aus nationalen Komitees Experten und der Industrie
- Allgemeine europäische Grenzwerte
- Harmonisierung bestehende Grenzwerte
- Technologie der in vitro Testung
- Qualitätsstandards
- Epidemiologie antimikrobieller Resistenz
- Internationale Zusammenarbeit
- Training Programme

National Antimicrobial Susceptibilty Testing Committees (NAC)

- Australian NAC
- British Society for Antimicrobial Chemotherapy (BSAC)
- Committé Antibiogramme - Société Française de Microbiologie (CA-SFM)
- Dutch Working Group on Antibiotics (SWAB)
- NAK Deutschland. During the period 2001 - 2011 Germany was represented by DIN and provided strong support in the work to establish EUCAST and the process through which harmonisation of breakpoints in Europe was achieved.
- Dutch Working Group on Antibiotics (SWAB)
- Estonian EUCAST Working group
- The Irish Antimicrobial Susceptibility Testing group
- Norwegian Working group on Antibiotics (NWGA)
- Swedish Reference Group for Antibiotics (SRGA)
- Swiss society for Microbiology

EMEA SOP for setting breakpoints through EUCAST

European Medicines Agency
Standard Operating Procedure

Title: Harmonisation of European Breakpoints set by EMEA/CHMP and EUCAST		Document no.: SOP/H/3043
Applies to: Product Team Leaders in the Human Pre-Authorisation Unit, (Co)Rapporteurs, External Experts, EUCAST		Effective Date: 14 February 2005
PUBLIC		Review Date: 14 February 2007
		Supersedes: N/A
Prepared by	Approved by	Authorised for issue by
Name: Bo Aronsson	Name: Agnès Saint Raymond	Name: Patrick Le Courtois
Signature: On file	Signature: On file	Signature: On file
Date: 10 Feb 05	Date: 10 Feb 05	Date: 10 Feb 05

1. Purpose

To describe the interaction between EMEA/CHMP and EUCAST in the process of harmonisation of European breakpoints.

Available from the EUCAST (www.eucast.org) and EMEA websites

EUCAST breakpoint tables available at http://www.eucast.org

Aminoglycosides - EUCAST clinical MIC breakpoints 2006-01-31

Aminoglycosides[1] Click on antibiotic name to see wild type MIC distributions.	Species-related breakpoints (S≤/R>)											Non-species related breakpoints[5] S≤/R>
	Enterobacteriaceae	*Pseudomonas*[2]	*Acinetobacter*[2]	*Staphylococcus*	*Enterococcus*[3]	*Streptococcus A,B,C,G*	*S.pneumoniae*	*H.influenzae M.catarrhalis*	*N.gonorrhoeae*	*N.meningitidis*	*Gram-negative anaerobes*	
Amikacin	8/16	8/16	8/16	8/16[4]	--	--	--	IE	--	--	--	8/16
Gentamicin	2/4	4/4	4/4	1/1	--	--	--	IE	--	--	--	2/4
Netilmicin	2/4	4/4	4/4	1/1	--	--	--	IE	--	--	--	2/4
Tobramycin	2/4	4/4	4/4	1/1	--	--	--	IE	--	--	--	2/4

1. The aminoglycoside breakpoints are based on modern once-daily administration of high aminoglycoside dosages. Most often aminoglycosides are given in combination with beta-lactam agents. For unlisted aminoglycosides refer to breakpoints determined by national breakpoint committees.
2. The S/I breakpoint has been increased from 2 to 4 mg/L for agents other than amikacin to avoid dividing the wild type MIC distribution. Thus there is no intermediate category for *Pseudomonas* species and *Acinetobacter* species.
3. *Enterococcus* spp - aminoglycoside monotherapy is ineffective against enterococci. There is synergism between aminoglycosides and betalactams in enterococci without acquired resistance mechanisms. There is no synergistic effect in enterococci with high level aminoglycoside resistance, i.e with gentamicin MIC>128 mg/L.
4. Resistance to amikacin and kanamycin is most reliably determined using kanamycin as test substance.
5. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not recommended (marked with -- or **IE** in the table).

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

Version*	Date	Action
1.2	2006-01-31	Added an explanation of links from antibiotic names to wild type MIC distributions. Revised footnotes. Table version number added.
1.1	2004-04-30	European aminoglycoside breakpoints harmonised by EUCAST.

**The number before the point indicates breakpoint change. The number after the point indicates minor changes (footnotes, spelling, format, etc) without a change of breakpoints.*

EUCAST breakpoint tables available at http://www.eucast.org

Aminoglycosides - EUCAST clinical MIC breakpoints 2006-01-31

Aminoglycosides[1] Click on antibiotic name to see wild type MIC distributions.	breakpoints (S≤/R>)							Non-species related breakpoints[5] S≤/R>
	Enterobac-riaceae	*S.pneu-moniae*	*H.influenzae M.catarrhalis*	*N.gonorr-hoeae*	*N.mening-itidis*	*Gram-negative anaerobes*	
Amikacin		--	IE	--	--	--	8/16
Gentamicin	2/4	--	IE	--	--	--	2/4
Netilmicin	2/4	--	IE	--	--		2/4
Tobramycin	2/4	--	IE	--			

Click on name to directly access MIC distributions

1. The aminoglycoside breakpoints are based on modern once-daily administration of high aminoglycoside dosages. Most often an … given in combination with beta-lactam agents. For unlisted aminoglycosides refer to breakpoints determined by national breakpoint committees.
2. The S/I breakpoint has been increased from 2 to 4 mg/L for agents other than amikacin to avoid div… *Pseudomonas* species and *Acinetobacter* species.
3. *Enterococcus* spp - aminoglycoside monotherapy is ineffective against enterococci. There is syner… ed resistance mechanisms. There is no synergistic effect in enterococci with high level aminoglycoside resistance, i.e with gent…
4. Resistance to amikacin and kanamycin is most reliably determined using kanamycin as test subst…
5. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are … species that have not been given a species-specific breakpoint and not for those species where susceptibility testing is not rec…

"…ashed" – laboratories are …commended not to test … against this species

-- = Susceptibility testing not recommended as the species is a poor target for therapy with the drug.
IE = There is insufficient evidence that the species in question is a good target for therapy with the drug.

Version*	Date	Action
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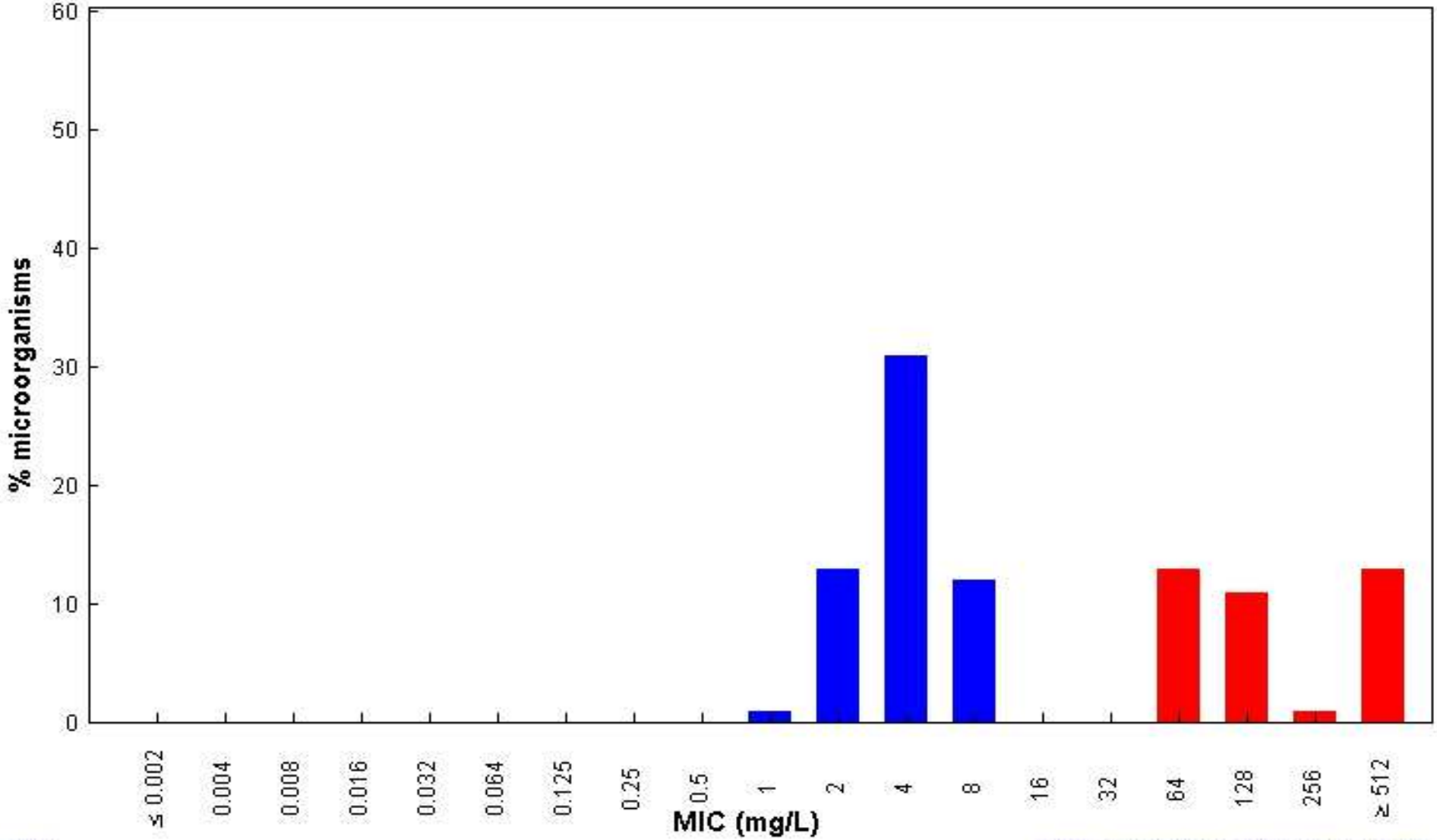
**The number before the point indicates breakpoint change. The number after the point indicates minor changes (foot… change of breakpoints.*

Insufficient evidence

Amoxicillin / Escherichia coli

EUCAST MIC Distribution - Reference Database 2010-11-22

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



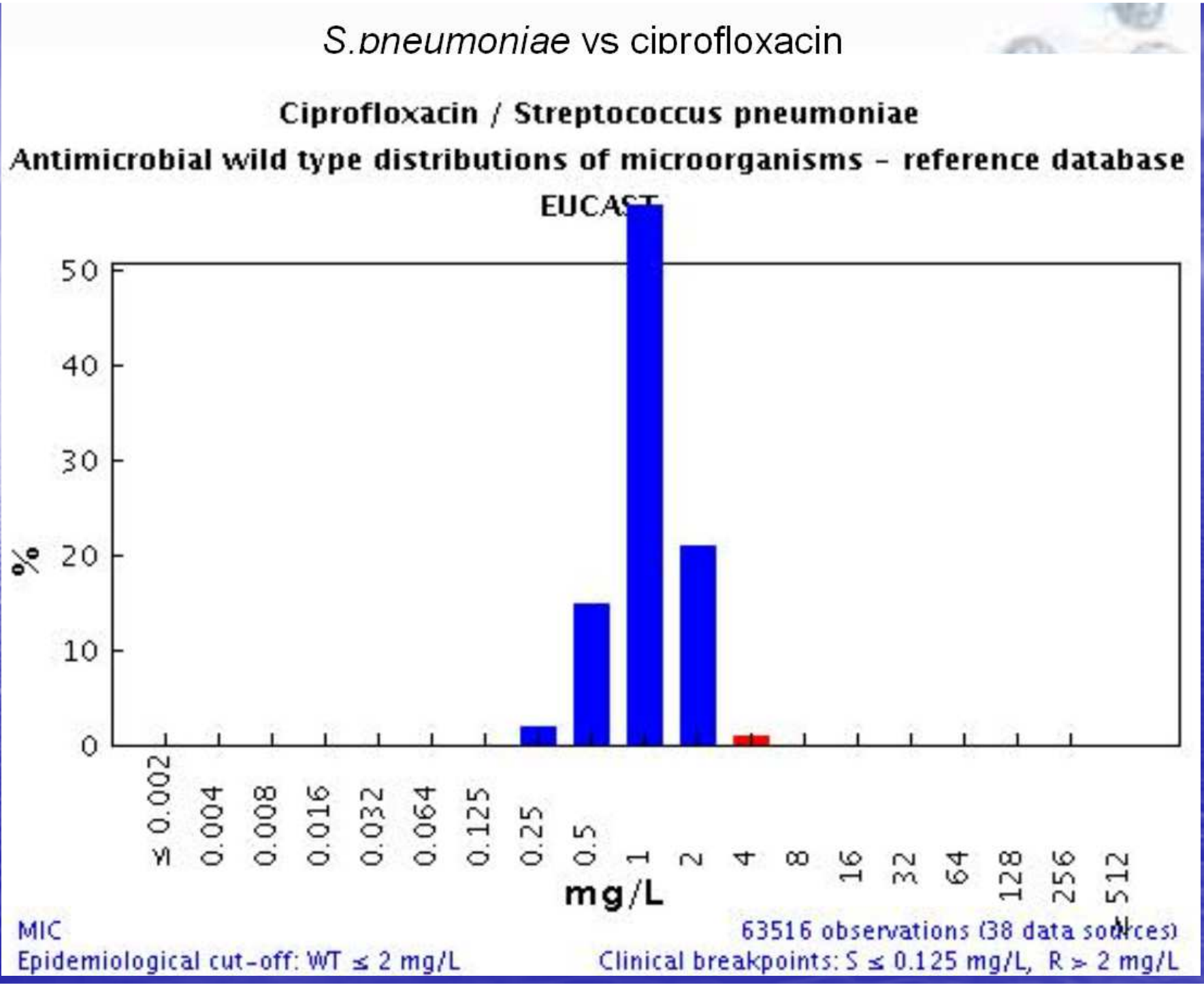
MIC

Epidemiological cut-off: WT ≤ 8 mg/L

5277 observations (20 data sources)

Clinical breakpoints: S ≤ - mg/L, R > 8 mg/L

S.pneumoniae vs ciprofloxacin



S.pneumoniae vs ciprofloxacin

	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
Ciprofloxacin	0	0	0	0	0	0	1	4	28	52	16	0	0	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	0	0	55	1191	671	101	21	2	0	2	3	0	0
Ciprofloxacin	0	0	0	0	0	0	0	4	45	363	454	119	11	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	0	2	2	15	32	2	0	1	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	3	80	256	61	11	1	1	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	1	5	64	155	17	4	0	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	1	4	35	130	51	3	0	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	1	197	251	41	10	1	0	1	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	1	16	125	102	28	3	0	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	1	8	96	209	59	1	2	0	0	1	0	0	0
Ciprofloxacin	0	0	0	0	0	0	3	20	92	69	10	3	1	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	2	5	161	544	64	10	0	2	1	0	0	0	0
Ciprofloxacin	0	0	0	0	6	4	4	13	245	854	379	9	6	1	1	1	0	0	0
Ciprofloxacin	0	0	0	0	3	0	2	22	225	917	401	16	3	2	4	1	0	0	0
Ciprofloxacin	0	0	0	0	0	1	3	9	426	933	138	11	5	2	1	0	2	0	0
Ciprofloxacin	0	0	0	0	2	0	3	13	402	1193	222	19	10	0	6	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	0	2	75	366	182	30	4	0	0	2	0	0	0
Ciprofloxacin	0	0	0	0	0	0	0	2	36	409	186	29	2	1	1	1	0	0	0
Ciprofloxacin	0	0	0	0	0	0	0	2	207	1052	225	22	2	10	0	1	0	0	0
Ciprofloxacin	0	0	0	0	6	7	25	130	2195	10500	4618	144	67	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	8	10	47	176	95	21	1	2	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	0	2	302	1777	786	102	1	6	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	2	103	335	58	11	0	1	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	1	7	100	265	26	5	0	1	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	1	1	4	35	130	51	3	0	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	8	37	60	16	1	0	0	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	3	20	228	280	49	11	1	1	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	0	15	122	99	28	3	1	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	1	10	120	331	78	2	2	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	2	3	27	155	111	18	4	1	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	0	0	50	544	149	23	2	0	1	2	1	0	0
Ciprofloxacin	0	0	0	0	0	4	4	10	181	256	74	6	2	0	1	0	0	0	0
Ciprofloxacin	0	0	8	13	9	8	4	34	77	210	76	9	18	1	0	0	0	3	0
Ciprofloxacin	0	0	0	0	0	1	0	14	120	272	96	8	0	2	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	0	66	85	31	2	1	4	0	0	0	0	0	228
Ciprofloxacin	0	0	0	0	0	0	0	0	1	65	150	18	4	0	1	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	1	2	41	99	55	11	1	0	0	0	0	0	0
Ciprofloxacin	0	0	0	0	0	0	0	422	2706	13072	3987	320	68	31	82	62	0	0	0

Wildtyp Verteilungen

- Referenz für epidemiologische „cut-off“ Werte
- Referenz zur Erstellung klinischer Grenzwerte
- Internationale Referenz zur Einstellung von Testmethoden

Definitionen

- Susceptible (Sensibel) S≤ x mg/L
- Intermediate (Intermediär)
- Resistant (Resistent) R> ymg/ L
- Wildtyp
- Nicht Wildtyp – **epidemiological cut-off value (ECOFF)**

EUCAST

- Langer wissenschaftlicher Prozess zur Grenzwertfindung
- Zusammenarbeit mit Gremien, Experten und Industrie
- Keine Industrie bei der Entscheidung
- Einheitliche Grenzwerte für alle Europäischen Länder
- Zusammenarbeit mit außereuropäischen Gremien
- Basiert auf einheitlicher Methode
- Daten sind für Jedermann zugänglich
- Datenbank für Expertenregeln