HELIOS Kliniken
Jeder Moment ist Medizin

Der Weg von CLSI zu EUCAST

Michael Lefmann, 25.03.2013

Von CLSI zu EUCAST

- Resistenztestung
- Entscheidung für EUCAST
- Implementierung
- Resistenzstatistik

Der „wahre“ Breakpoint ???

Table 1. Similarities and differences in international breakpoint systems—current cefotaxime and ciprofloxacin breakpoints for Enterobacteriaceae in Europe and the USA

Breakpoint committee (country)	Cefotaxime breakpoint (mg/L)		Ciprofloxacin breakpoint (mg/L)	
	susceptible	resistant	susceptible	resistant
BSAC (UK)	≤2	≥4	≤1	≥2
CA-SFM (France)	≤4	>32	≤1	>2
CRG (Netherlands)	≤4	>16	≤1	>2
DIN (Germany)	≤2	≥16	≤1	≥4
NCCLS (USA)	≤8	≥64	≤1	≥4
NWGA (Norway	≤1	≥32	≤0.12	≥4
SRGA (Sweden)	≤0.5	≥2	≤0.12	≥2

Kahlmeter et al. JAC2003(52):145-8

EUCAST presentation, CLSI, Boston, July 2009.

E.coli, Klebsiella, Proteus

EUCAST vs. CLSI

Antimicrobial	EUCAST S≤/R> (mg/L)	CLSI S≤/R> (mg/L)
Ampicillin	8 / 8	8 / 16
Cefotaxime	1 / 2	8 / 32
Ceftazidime	2 / 8	8 / 16
Cefuroxime	8* / 8	4 / 16
Imi-/Meropenem	2 / 8	4 / 8
Ciprofloxacin	0.5 / 1	1 / 2
Gentamicin/Tobra	2 / 4	4 / 8
Amikacin	8 / 16	16 / 32
Trimethoprim	2 / 4	8 / 8
Nitrofurantoin	64 / 64	32 / 64

*Increased from 4 to 8 mg/L to avoid dividing the wild type MIC distribution

EUCAST presentation, CLSI, Boston, July 2009.

P. aeruginosa
EUCAST vs. CLSI

Antimicrobial	EUCAST S≤/R> (mg/L)	CLSI S≤/R> (mg/L)
Ceftazidime	8 / 8	8 / 16
Piperacillin(tzb)	16 / 16	64 / 64
Imipenem	4 / 8	4 / 8
Ciprofloxacin	0.5 / 1	1 / 2
Genta/Tobra	4 / 4	4 / 8

EUCAST - CLSI bei Enterobakterien

	Bewertung - MHK (mg/l)							
	CLSI 2009			CLSI 2010			EUCAST	
	S	I	R	S	I	R	S	R
Cefazolin	≤8	16	≥32	≤1	2	≥4	--	--
Cefuroxim	≤4	8-16	≥32	≤4	8-16	≥32	≤8	>8
Cefotaxim	≤8	16-32	≥64	≤1	2	≥4	≤1	>2
Ceftazidim	≤8	16	≥32	≤4	8	≥16	≤1	>4
Cefepime	≤8	16	≥32	≤8	16	≥32	≤1	>4
Ampicillin	≤8	16	≥32	≤8	16	≥32	--	8
Am/Sulb	≤8	16	≥32	≤8	16	≥32	--	8
Piperacillin	≤16	32-64	≥128	≤16	32-64	≥128	≤8	>16
Pip/Taz	≤16	32-64	≥128	≤16	32-64	≥128	≤8	>16

Becton Dickinson Somer 2010:

Mit den zurzeit vorhandenen CLSI-Panels ist aufgrund der vorhandenen Antibiotika-Konzentrationen eine Bewertung nach CLSI 2010 nicht möglich.

Solange die FDA die neuen Breakpoints nicht übernommen habe, seien sie nicht „mandatory“.

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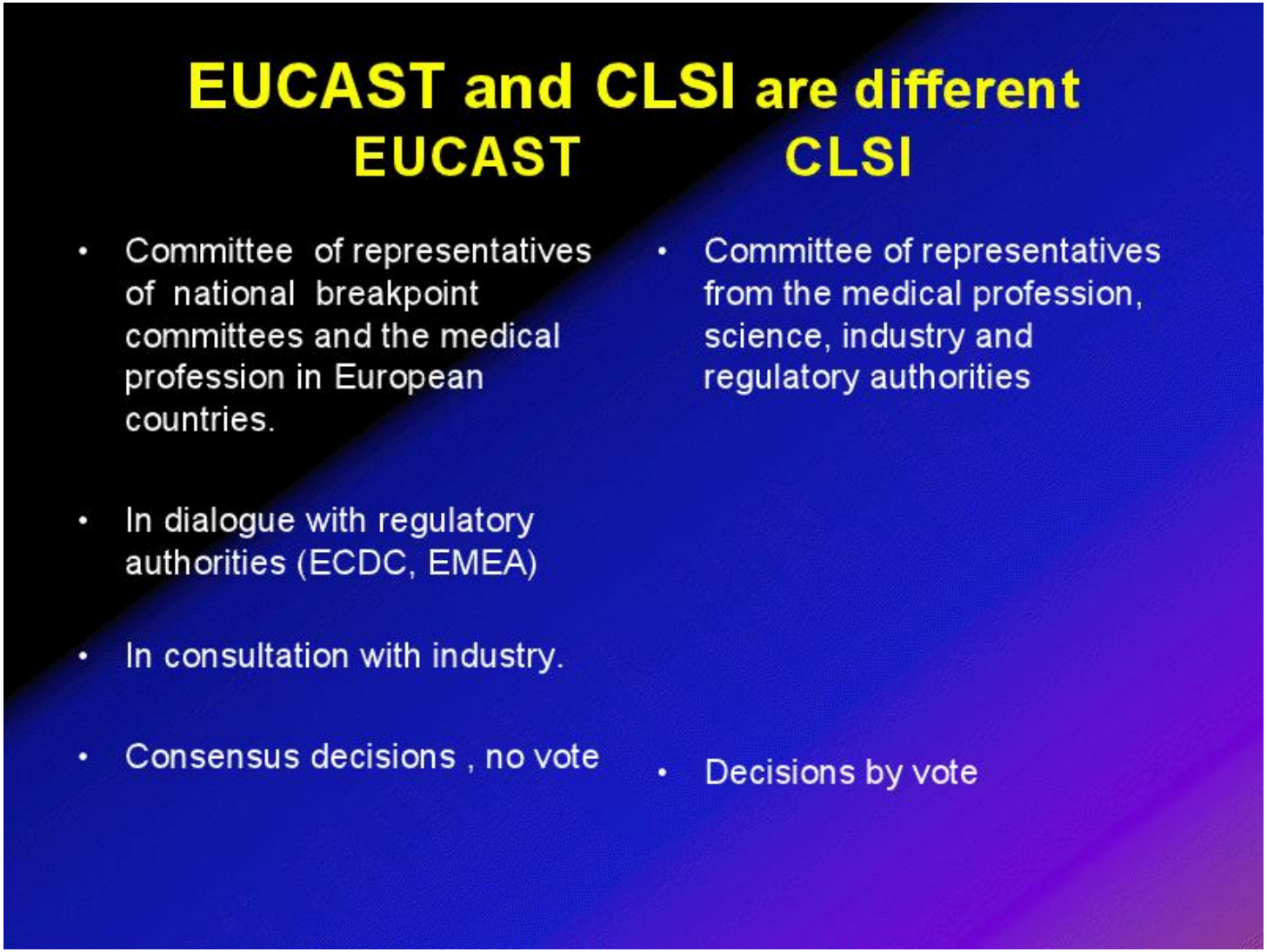
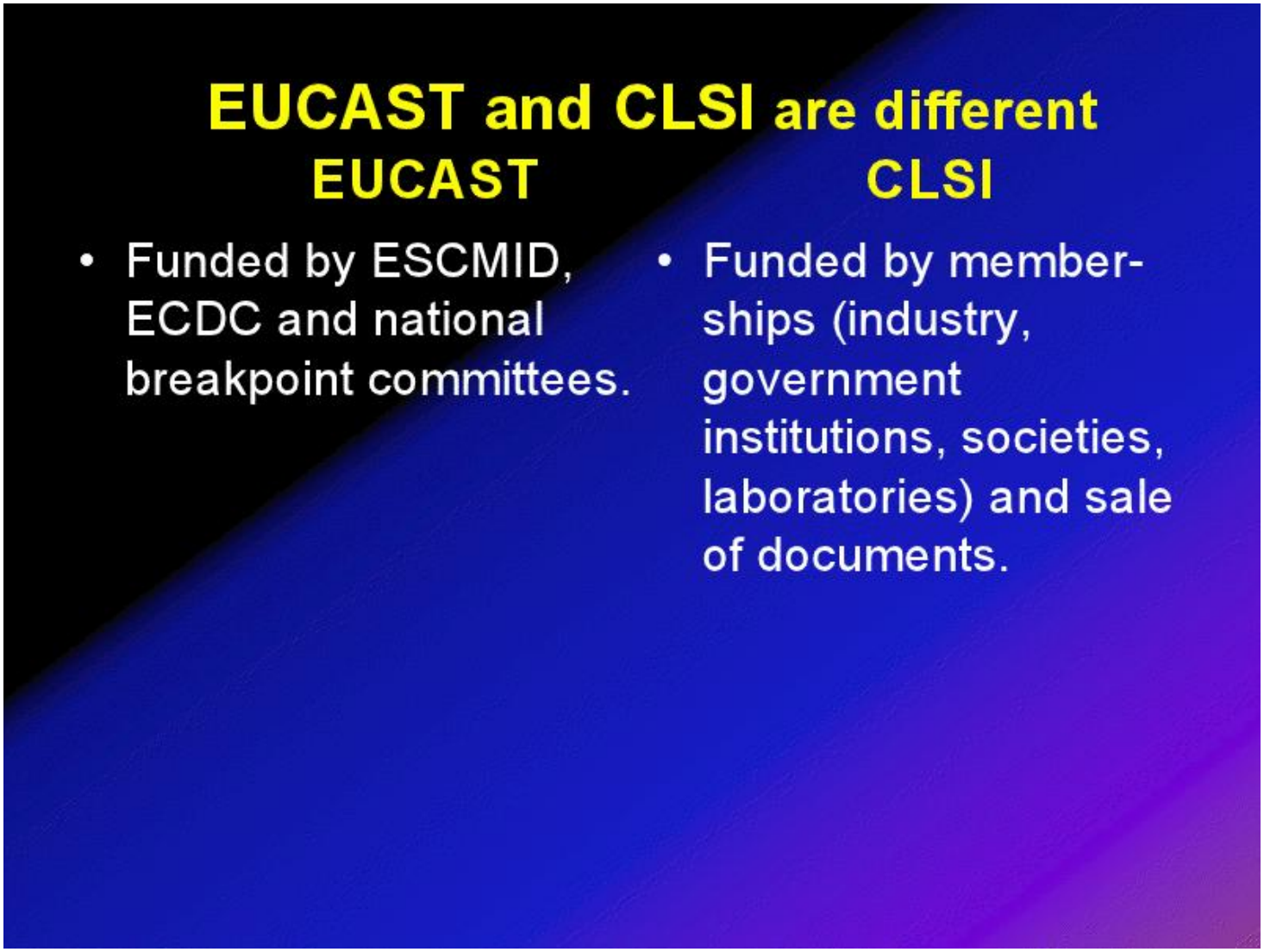
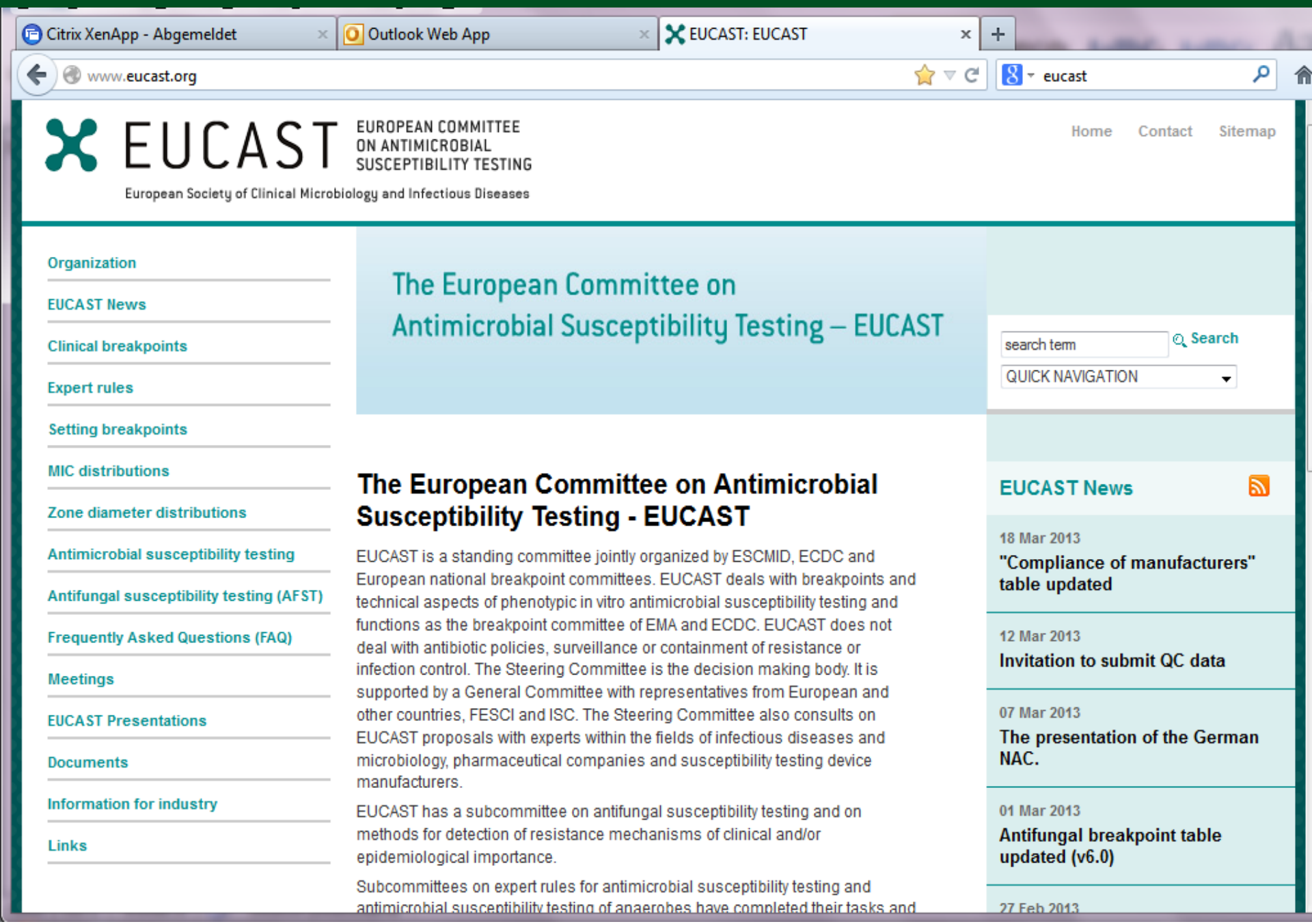
EUCAST presentation, CLSI, Boston, July 2009.



EUCAST presentation, CLSI, Boston, July 2009.

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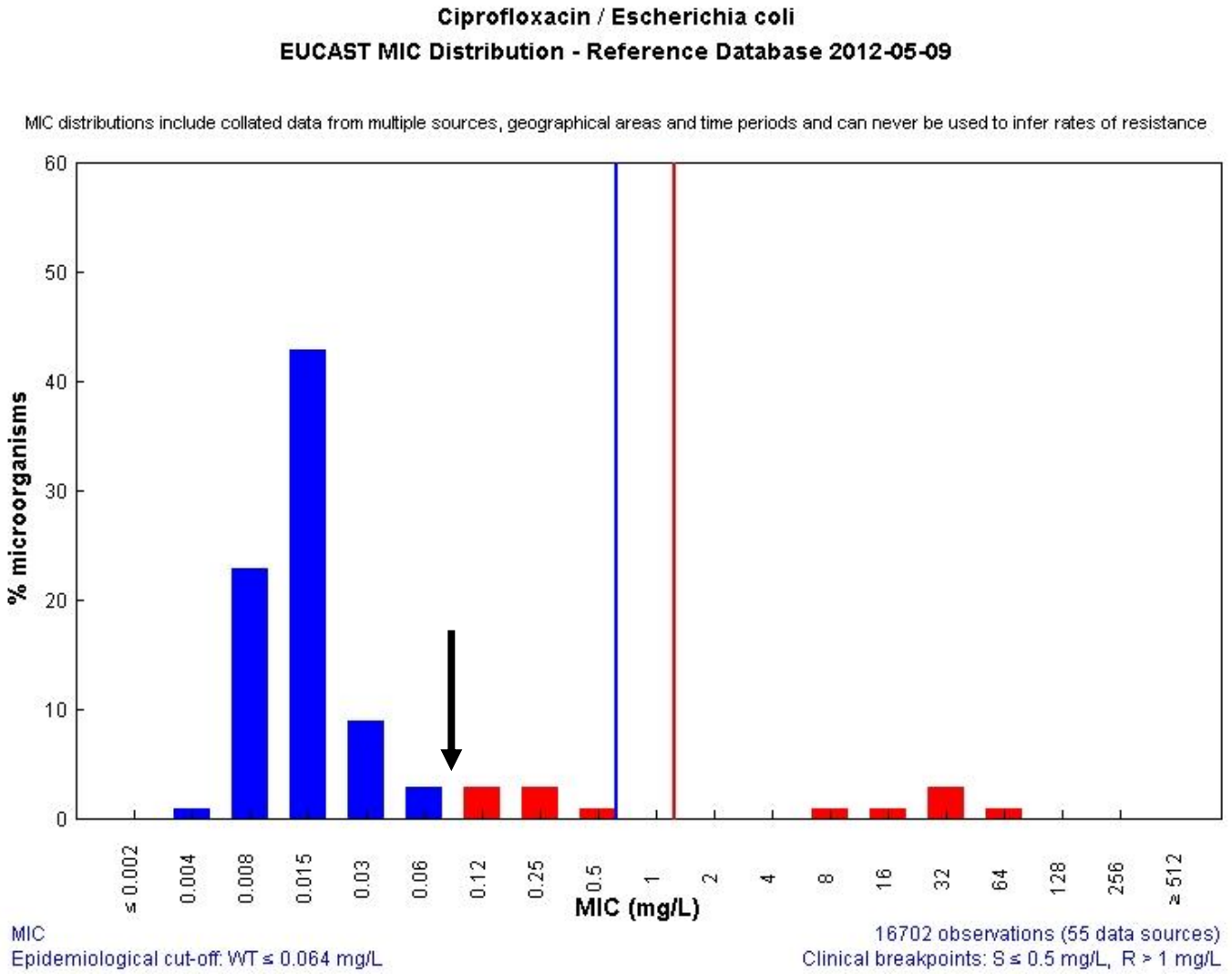
The European Committee on Antimicrobial Susceptibility Testing - EUCAST
EUCAST is a standing committee jointly organized by ESCMID, ECDC and European national breakpoint committees. EUCAST deals with breakpoints and technical aspects of phenotypic in vitro antimicrobial susceptibility testing and functions as the breakpoint committee of EMA and ECDC. EUCAST does not deal with antibiotic policies, surveillance or containment of resistance or infection control. The Steering Committee is the decision making body. It is supported by a General Committee with representatives from European and other countries, FESCI and ISC. The Steering Committee also consults on EUCAST proposals with experts within the fields of infectious diseases and microbiology, pharmaceutical companies and susceptibility testing device manufacturers.
EUCAST has a subcommittee on antifungal susceptibility testing and on methods for detection of resistance mechanisms of clinical and/or epidemiological importance.
Subcommittees on expert rules for antimicrobial susceptibility testing and antimicrobial susceptibility testing of anaerobes have completed their tasks and
EUCAST News
18 Mar 2013
"Compliance of manufacturers" table updated
12 Mar 2013
Invitation to submit QC data
07 Mar 2013
The presentation of the German NAC.
01 Mar 2013
Antifungal breakpoint table updated (v6.0)
27 Feb 2013

Resistenztestung

- Vorteile durch EUCAST
  - Breakpoints
    - MHK-Verteilung der Wildtypen => Epidemiologische cut-offs
      - » Erlaubt das Erkennen neuer Resistenzmechanismen
    - Klinische Breakpoints (S/I/R) => wahrscheinliche Wirksamkeit

MHK – Verteilung



http://mic.eucast.org/Eucast2/

Resistenztestung mit EUCAST

- Vorteile durch EUCAST
  - Breakpoints
    - MHK-Verteilung der Wildtypen => Epidemiologische cut-offs
      - » Erlaubt das Erkennen neuer Resistenzmechanismen
    - Klinische Breakpoints (S/I/R) => wahrscheinliche Wirksamkeit
  - Expertenregeln
    - Darstellung der intrinsischen Resistenzen auch gegen Nicht-ß-Laktame
    - Einheitliche Bewertung der Resistenzergebnisse

EUCAST neue Expert-Regeln 2.0 (29.10.2011)

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Article type : Invited Review

EUCAST Expert Rules in Antimicrobial Susceptibility Testing

Roland Leclercq[1,2], Rafael Cantón[2,3,4*], Derek F.J. Brown[4], Christian G. Giske[2,4,5], Peter Heisig[2,6], Alasdair P. MacGowan[4,7], Johan W. Mouton[4,8], Patrice Nordmann[2,9], Arne C. Rodloff[4,10], Gian Maria Rossolini[2,11], Claude-James Soussy[4,12], Martin Steinbakk[4,13], Trevor G. Winstanley[2,14], and Gunnar Kahlmeter[4,15]

Intrinsische Resistenzen in Enterobakterien

Table 1. Intrinsic resistance in Enterobacteriaceae. Enterobacteriaceae are also intrinsically resistant to benzylpenicillin, glycopeptides, fusidic acid, macrolides (with some exceptions[1]), lincosamides, streptogramins, rifampicin, daptomycin and linezolid.

Rule no.	Organisms	Ampicillin	Amoxicilin-clavulanate	Ticarcillin	Piperacillin	Cefazolin	Cefoxitin	Cefamandole	Cefuroxime	Aminoglycosides	Tetracyclines/ tigecycline	Polymyxin B/ Colistin	Nitrofurantoin
1.1	*Citrobacter koseri*	R		R	R								
1.2	*Citrobacter freundii*	R	R			R	R						
1.3	*Enterobacter cloacae*	R	R			R	R						
1.4	*Enterobacter aerogenes*	R	R			R	R						
1.5	*Escherichia hermannii*	R		R									
1.6	*Hafnia alvei*	R	R			R							
1.7	*Klebsiella* spp.	R		R									
1.8	*Morganella morganii*	R	R			R			R		R	R	R
1.9	*Proteus mirabilis*										R	R	R
1.10	*Proteus vulgaris*	R				R		R	R		R	R	R
1.11	*Proteus penneri*	R				R		R	R		R	R	R
1.12	*Providencia rettgeri*	R	R			R					R	R	R
1.13	*Providencia stuartii*	R	R			R				Note[2]	R	R	R
1.14	*Serratia marcescens*	R	R			R		R	R	Note[3]		R	R
1.15	*Yersinia enterocolitica*	R	R	R		R	R	R					
1.16	*Yersinia pseudotuberculosis*											R	

Intrinsische Resistenzen in Nonfermentern

Table 2. Intrinsic resistance in non-fermentative Gram-negative bacteria. Non-fermentative Gram-negative bacteria are also intrinsically resistant to benzylpenicillin, cefoxitin, cefamandole, cefuroxime, glycopeptides, fusidic acid, macrolides, lincosamides, streptogramins, rifampicin, daptomycin and linezolid

Rule no.	Organisms	Ampicillin	Amoxicillin-Clavulanate	Ticarcillin	Ticarcillin-clavulanate	Piperacillin	Piperacillin-tazobactam	Cefazolin	Cefotaxime	Ceftriaxone	Ceftazidime	Ertapenem	Imipenem	Meropenem	Ciprofloxacin	Chloramphenicol	Aminoglycosides	Trimethoprim	Trimethoprim-sulfamethoxazole	Fosfomycin	Tetracyclines/ Tigecycline	Polymyxin B/ Colistin
2.1	*Acinetobacter baumannii, Acinetobacter calcoaceticus*	R[1]	R[1]					R	R	R		R						R		R		
2.2	*Achromobacter xylosoxydans*	R						R	R	R		R										
2.3	*Burkholderia cepacia* complex[2]	R	R	R	R			R				R	R		R	R	R[3]	R		R		R
2.4	*Elizabethkingia meningoseptica*	R		R	R			R	R	R	R	R	R	R								R
2.5	*Ochrobactrum anthropi*	R	R	R	R	R	R	R	R	R	R	R										
2.6	*Pseudomonas aeruginosa*	R	R					R	R	R		R				R	Note[4]	R[5]	R[5]		R	
2.7	*Stenotrophomonas maltophilia*	R	R	R		R	R	R	R	R	R[6]	R	R	R			R[3]	R[7]		R		

R = resistant

[1] *Acinetobacter baumannii* may appear susceptible to ampicillin-sulbactam due to activity of sulbactam against this species.

[2] *Burkholderia cepacia* complex includes different species. Some strains may appear susceptible to some β-lactams *in vitro* but they are clinically resistant and are shown as R in the table.

[3] *Burkholderia cepacia* and *Stenotrophomonas maltophilia* are intrinsically resistant to all aminoglycosides. Intrinsic resistance is attributed to poor permeability and putative efflux. In addition, most *Stenotrophomonas maltophilia* produce the AAC(6')Iz enzyme.

[4] *Pseudomonas aeruginosa* is intrinsically resistant to kanamycin and neomycin due to low level APH(3')-IIb activity.

[5] *Pseudomonas aeruginosa* typically is resistant to trimethoprim and moderately susceptible to sulfonamides. Although it may appear susceptible *in vitro* to trimethoprim-sulfamethoxazole, it should be considered resistant.

[6] *Stenotrophomonas maltophilia* may show low ceftazidime MIC values but should be considered resistant.

[7] *Stenotrophomonas maltophilia* typically is susceptible to trimethoprim-sulfamethoxazole, but resistant to trimethoprim alone.

Enterobacteriaceae

EUCAST Clinical Breakpoint Table v. 3.1, valid from 2013-02-11

Disk diffusion (EUCAST standardised disk diffusion method)
Medium: Mueller-Hinton agar
Inoculum: McFarland 0.5
Incubation: Air, 35±1°C, 18±2h
Reading: Read zone edges as the point showing no growth viewed from the back of the plate against a dark background illuminated with reflected light.
Quality control: *Escherichia coli* ATCC 25922

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
Benzylpenicillin	-	-		-	-	
Ampicillin	8[1]	8	10	14[A,B]	14[B]	**1/A.** Wild type Enterobacteriaceae are categorised as susceptible to aminopenicillins. Some countries prefer to categorise wild type isolates of *E. coli* and *P. mirabilis* as intermediate. When this is the case, use the MIC breakpoint S ≤ 0.5 mg/L and the corresponding zone diameter breakpoint S ≥ 50 mm. **B.** Ignore growth that may appear as a thin inner zone on some batches of Mueller-Hinton agars.
Ampicillin-sulbactam	8[1,2]	8[2]	10-10	14[A,B]	14[B]	**2.** For susceptibility testing purposes, the concentration of sulbactam is fixed at 4 mg/L.
Amoxicillin	8[1]	8	-	Note[C]	Note[C]	**C.** Susceptibility inferred from ampicillin.
Amoxicillin-clavulanate	8[1,3]	8[3]	20-10	17[A,B]	17[B]	**3.** For susceptibility testing purposes, the concentration of clavulanate is fixed at 2 mg/L.
Piperacillin	8	16	30	20	17	
Piperacillin-tazobactam	8[4]	16[4]	30-6	20	17	**4.** For susceptibility testing purposes, the concentration of tazobactam is fixed at 4 mg/L.
Ticarcillin	8	16	75	23	23	
Ticarcillin-clavulanate	8[3]	16[3]	75-10	23	23	
Phenoxymethylpenicillin	-	-		-	-	
Oxacillin	-	-		-	-	
Cloxacillin	-	-		-	-	
Dicloxacillin	-	-		-	-	
Flucloxacillin	-	-		-	-	
Mecillinam (uncomplicated UTI only)	8[5]	8[5]	10	15[E,F]	15[E,F]	**5/E.** Mecillinam (pivmecillinam) breakpoints relate to *E. coli, Klebsiella* spp. and *P. mirabilis* only. **F.** Ignore isolated colonies within the inhibition zone for *E. coli*.

Cephalosporins[1]	MIC breakpoint (mg/L)	Disk content	Zone diameter breakpoint	Notes Numbers for comments on MIC breakpoints

Content | Notes | Changes | Enterobacteriaceae | Pseud | S.maltophilia | Acinetob | Staphs | Enterococcus | Strept A,B,C,G | Pneumo | Viridans strept | H.in

Von CLSI zu EUCAST

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Resistenztestung (CLSI) – vor Umstellung

Phönix

- Gram-neg. Panel NMIC/ID-64
- Gram-pos. Panel PMIC/ID-65
- Streptokoken Panel SMIC/ID-9

MHK mit E-Testen

- Bestätigung VRE, Stenotrophomonas, Helicobacter, Pen-Resistenz bei Pneumokoken u. Streptokokken, etc.

Agardiffusion

- Streptokokken, Hämophilus, Moraxella, (MR-)Pseudomonas, Nonfermenter, etc.

MHK für Sproßpilze (E-Test, Mikroboullion)

EUCAST – Vorbereitung

- Vorbereitung der Umstellung Monate vorher
  - Information und Schulung der MTAs
  - Automatisiertes Testsystem
    - Updates, neue Untersuchungs-Panel, Anpassung des Regelwerks
  - Agardiffusionstest
    - Medien und AD-Plättchen mit EUCAST-Beladung (verschiedene Hersteller)
    - Anpassung der Methoden zur Qualitätssicherung
    - Unterschiede zu bekannten Verfahren hervorheben
      (Plättchenbeladung, Medien, Beurteilung der HH, etc.)
  - Erstellung neuer Dokumente (Akkreditierung)

EUCAST – Implementierung

- Veränderte Antibiogramme
  - Phönix
    - z.B. Ableitung der Ergebnisse für Aminop/Inhib von Ampicillin für Enterokoken im LIS
  - Agardiffusionsteste
    - Vergleich der Plättchenbeladung und ggf. Anpassung
      - » Ampicillin für Enterokokken, Streptokokken, Hämophilus 2µg
      - » Ampicillin für Enterobakterien 10µg

EUCAST – Qualitätskontrollen

- Agardiffusion
  - Einige AB lagen häufiger nicht im Range
  - Große interindividuelle Schwankungen bei Durchführung
  - Zeitweise bei wöchentlichen Kontrollen immer mal wieder Ausfälle

    (z.B. Ampicillin (2µg) bei *Hämophilus influenzae*
  - Einstellen des McFarland mit Densitometer sinnvoll
  - Probleme mit Plättchen-Chargen (Haltbarkeit, z.B. Meropenem)

EUCAST – Umstellung Februar 2011 (5 Labore)

- Info an die „Kunden“
- Umstellung an Tag „X“ im laufenden Betrieb
- Probleme bei automatisierter Resistenztestung
  - fehlende / falsche Grenzwerte im Gerät
  - fehlende Parameter in der Schnittstelle zum LIS
  - „neue Resistenzphänomene“ (Aminoglykosid-Resistenz bei Staphylokokken,…..)
- Lieferschwierigkeiten von Untersuchungs-Panel, AD-Testplättchen und Nährmedien

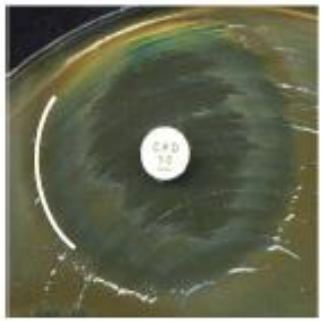
EUCAST – Offene Punkte

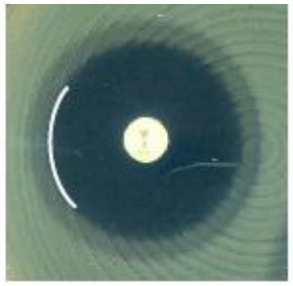
Fehlende Breakpoints (BP):

- Stenotrophomonas - BP nur für TMP/Sulfa (nicht Levofloxacin, Moxifloxacin, Ticarcillin/Clavulans.)
- Acinetobacter spp. - keine BP für Sulbactam u. Tigecyclin
- Andere Nonfermenter (Achromobacter, Burkholderia) – keine BP
- Corynebakterien, Bacillus spp. – keine BP
- ……

EUCAST – Schulung, Schulung, Schulung,….

Reading of zones with colonies within the zone.





E. coli CoNS *Moraxella* *Haemophilus*

EUCAST expert rules *v2*

2010

Ceftazidime and cefepime R breakpoint were reduced from >8 mg/L to >4 mg/L

Cefalosporins	EUCAST	
	S (≤)	R (>)
Cefotaxime	1	2
Ceftazidime	1	4
Cefepime	1	4

Report as found regardless of the presence of a resistance mechanism (ESBL or other)

Breakpoint tables for interpretation of MICs and zone diameters Version 1.3, January 5, 2011

1. The cephalosporin breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including ESBL and plasmid mediated AmpC). Some strains that produce beta-lactamases are susceptible or intermediate to 3rd or 4th generation cephalosporins with these breakpoints and should be reported as found, i.e. the presence or absence of an ESBL does not in itself influence the categorization of susceptibility. In many areas, ESBL detection and characterization is recommended or mandatory for infection control purposes.

R. Canton ECCMID 2011

Carbapenem breakpoints and Enterobacteriaceae

	FDA	CLSI (2010)*		EUCAST (EMEA) (2009)		
Enterobacteriaceae	**S**	**S**	**R**	**S**	**R**	**ECOFF**
Imipenem	≤4	≤1*	≥4*	≤2	>8	≤0,5; ≤1**
Meropenem	≤4	≤1*	≥4*	≤2	>8	≤0,125
Ertapenem	≤2	≤0.25*	≥1*	≤0,5	>1	≤0,06
Doripenem	≤0,5	≤1*	≥4*	≤1	>4	≤0,12

*M100-S20U June 2010 ***E. coli* y *K. pneumoniae***

Report as found regardless of the presence or absense of a carbapenemase

Breakpoint tables for interpretation of MICs and zone diameters Version 1.3, January 5, 2011

1. The carbapenem breakpoints for Enterobacteriaceae will detect all clinically important resistance mechanisms (including the majority of carbapenemases). Some strains that produce carbapenemase are categorized as susceptible with these breakpoints and should be reported as tested, i.e. the presence or absence of a carbapenemase does not in itself influence the categorization of susceptibility. In many areas, carbapenemase detection and characterization is recommended or mandatory for infection control purposes.

R. Canton ECCMID 2011

K. pneumoniae – OXA 48

	Ertapenem MHK [mg/l]		Imipenem MHK [mg/l]		Meropenem MHK [mg/l]	
	Phönix	**E-Test**	**Phönix**	**E-Test**	**Phönix**	**E-Test**
Pat. 1 BK	>1.0	1.0	>8.0	0.5	≤1.0	0.5
Pat. 2 BK	>1.0	4.0	2.0	2.0	≤1.0	2.0

Beide Pat. verstarben unter Imipenem-Therapie.

Pat. 2 hatte vor der pos. Bk bereits 10 Tage Imipenem erhalten.

NAC

- **Antimicrobial susceptibility testing**
  - Strategy at national level
  - Implementation of breakpoints and methods
  - Education (national workshops, websites)
  - Liaison and consultation with EUCAST (chairman or scientific secretary GC representative)
  - Liaison with groups involved in AMR-surveillance (ECDC, EARSS, ….).
  - QA
- Antimicrobial Policies
- Antimicrobial Resistance Surveillance
- Antimicrobial Consumption and Policies

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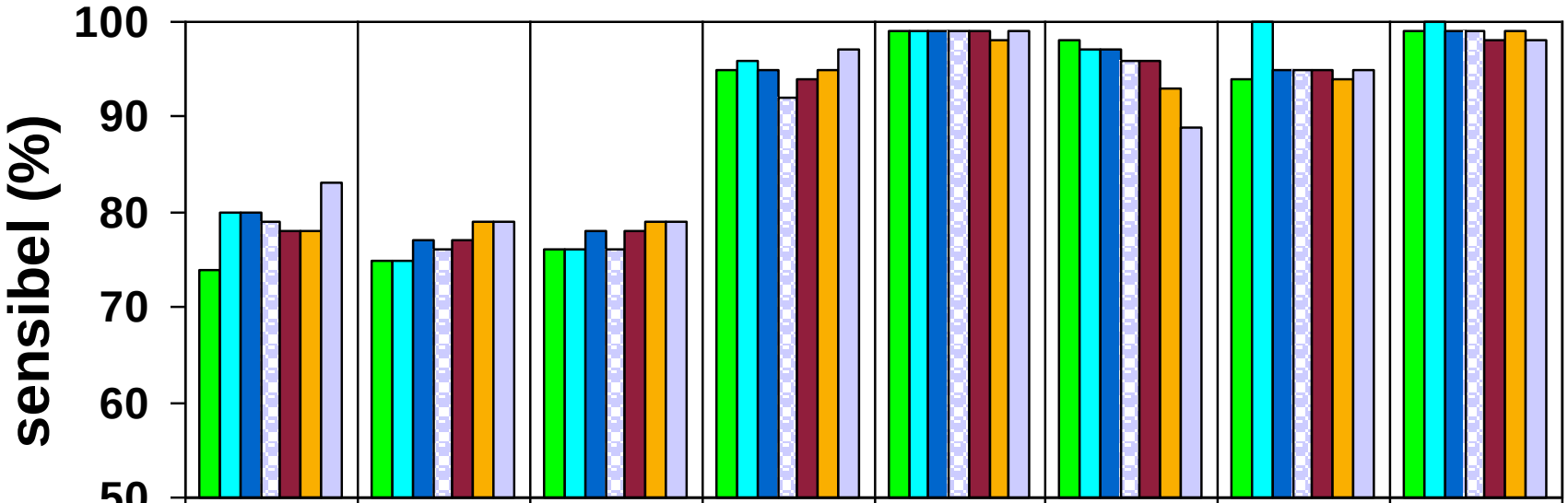
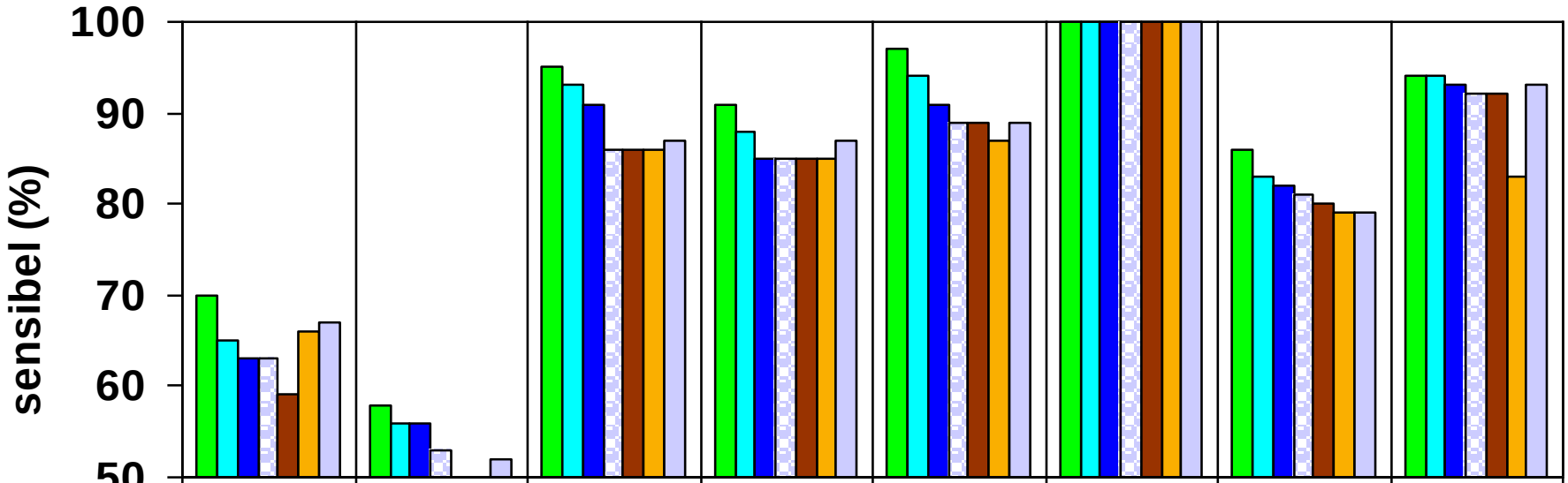
Staphylococcus aureus



	Oxacillin	Erythro-mycin	Clinda	Fosfo	Rifa	Genta	Doxy	TMP/ SXT
2006 (n=768)	74	75	76	95	99	98	94	99
2007 (n=731)	80	75	76	96	99	97	100	100
2008 (n=754)	80	77	78	95	99	97	95	99
2009 (n=910)	79	76	76	92	99	96	95	99
2010 (n=897)	78	77	78	94	99	96	95	98
2011 (n=804)	78	79	79	95	98	93	94	99
2012 (n=1014)	83	79	79	97	99	89	95	98

MRSA

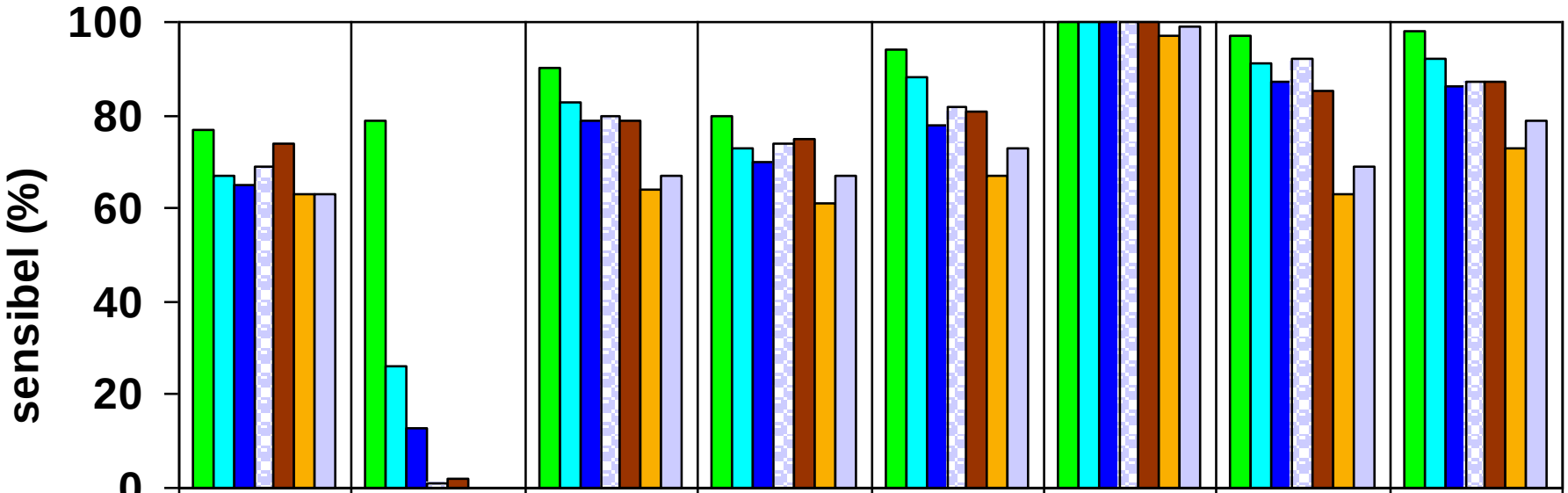
Escherichia coli



	Aminop./ Inhib.	Pipera-cillin	Pip./ Taz.	Cefuro-xim	Cefo-taxim	Imi-penem	Cipro-floxacin	Genta-micin
2006 (n=1099)	70	58	95	91	97	100	86	94
2007 (n=1181)	65	56	93	88	94	100	83	94
2008 (n=1282)	63	56	91	85	91	100	82	93
2009 (n=1662)	63	53	86	85	89	100	81	92
2010 (n=1851)	59	49	86	85	89	100	80	92
2011 (n=2017)	66	50	86	85	87	100	79	83
2012 (n=2301)	67	52	87	87	89	100	79	93

ESBL

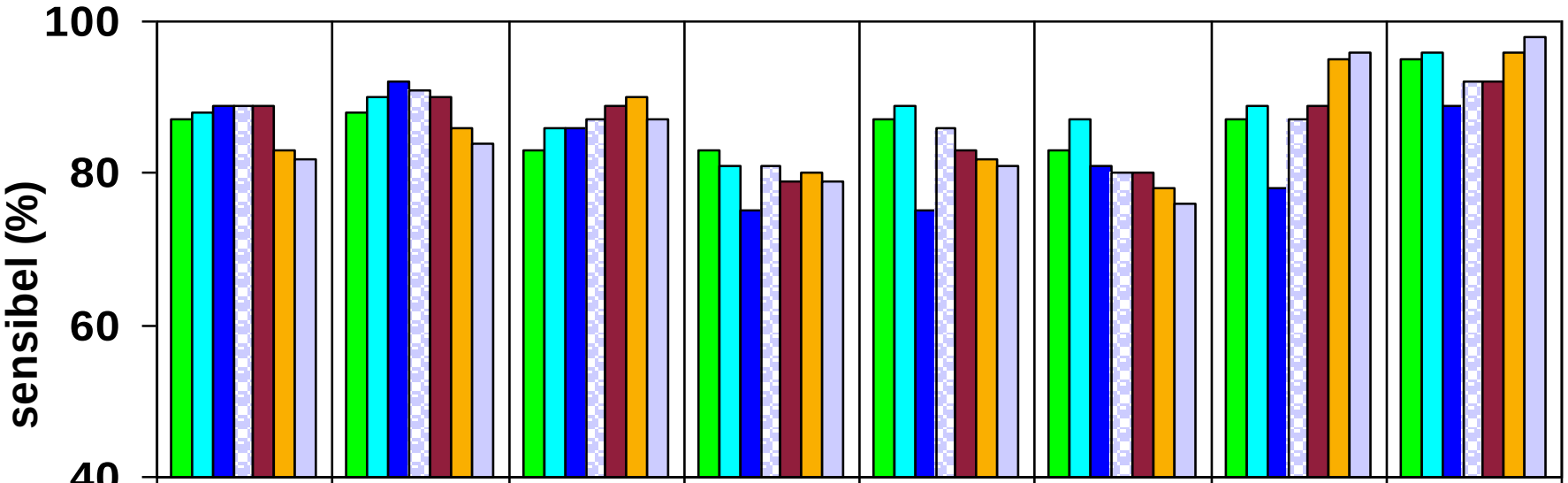
Klebsiella pneumoniae



	Aminop./ Inhib.	Pipera-cillin	Pip./ Taz.	Cefuro-xim	Cefo-taxim	Imi-penem	Cipro-floxacin	Genta-micin
2006 (n=202)	77	79	90	80	94	100	97	98
2007 (n=199)	67	26	83	73	88	100	91	92
2008 (n=268)	65	13	79	70	78	100	87	86
2009 (n=306)	69	1	80	74	82	100	92	87
2010 (n=330)	74	2	79	75	81	100	85	87
2011 (n=452)	63	0	64	61	67	97	63	73
2012 (n=557)	63	0	67	67	73	99	69	79

ESBL

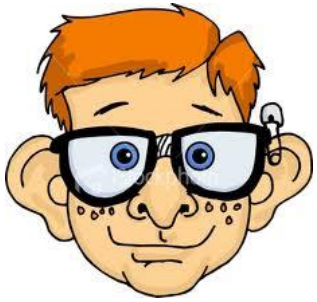
Pseudomonas aeruginosa



	Piperacillin	Pip./ Taz.	Ceft-azidim	Imi-penem	Mero-penem	Cipro- flox.	Genta-micin	Tobra-mycin
2006 (n=361	87	88	83	83	87	83	87	95
2007 (n=398)	88	90	86	81	89	87	89	96
2008 (n=414)	89	92	86	75	75	81	78	89
2009 (n=443)	89	91	87	81	86	80	87	92
2010 (n=487)	89	90	89	79	83	80	89	92
2011 (n=450)	83	86	90	80	82	78	95	96
2012 (n=554)	82	84	87	79	81	76	96	98

„Take home“

- **EUCAST hat sich in unserer Praxis bewährt. Die Vorteile – Transparenz, Verfügbarkeit, Plausibilität – überwiegen deutlich die Probleme bei der Umstellung im Routinebetrieb**










Jeder Moment ist Medizin

HELIOS Kliniken

Vielen Dank!

HELIOS Klinikum Emil von Behring

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