Société belge d'infectiologie et de microbiologie clinique
Belgische vereniging voor infectiologie en klinische microbiologie

30th Symposium : What will change in your daily practice with the new
Elewijt, 26-05-2008 EUCAST breakpoints for antibiotic susceptibility testing

Epidemiological consequences of new breakpoints

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26/05/08

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Epidemiological consequences of new breakpoints: Questions?

- What happens to antibiotic susceptibility data of epidemiologically important clinical isolates if the EUCAST breakpoints are applied ?
- Which species/antibiotic combinations are most affected?
- Would implementation of EUCAST breakpoints have consequences for:
  - Targeted therapy
  - Empiric therapeutic schemes

New breakpoints: How to predict influence on epidemiology?

- Breakpoints as presented in EUCAST tables can be directly applied to MIC distributions: local, national, international surveillance data:
  - Strains collected for MYSTIC study
    - European data
    - Belgian data
  - Results from reference center for ESBL's
- Individual hospital data
  - Automated susceptibility testing, Vitek, Phoenix, can be set-up with EUCAST breakpoints
  - Mostly disk diffusion data: no EUCAST breakpoints for agar diffusion available yet: MIC breakpoints to be extrapolated in DD zones (regression curves)

Influence of EUCAST breakpoints on epidemiology of Gram positives?

Major pathogens:

- *Staphylococcus aureus:*
  - no changes in oxa breakpoints: no epidemiological changes
- *Enterococci*:
  - VRE no problem in Belgium: prevalence < 1% in clinical isolates
- *Streptococcus pneumoniae*:
  - Up to now almost no strains with MIC >2 to penicillin have been isolated in Belgium (< 4% of resistant isolates)

  ⇒ No epidemiological changes

Reference lab for pneumococci, UZ Leuven

Influence of EUCAST breakpoints on epidemiology of Gram negatives?

Major challenges:

- Enterobacteriaceae
- ESBL-producing Enterobacteriaceae
- *Enterobacter cloacae*
- *Pseudomonas aeruginosa*

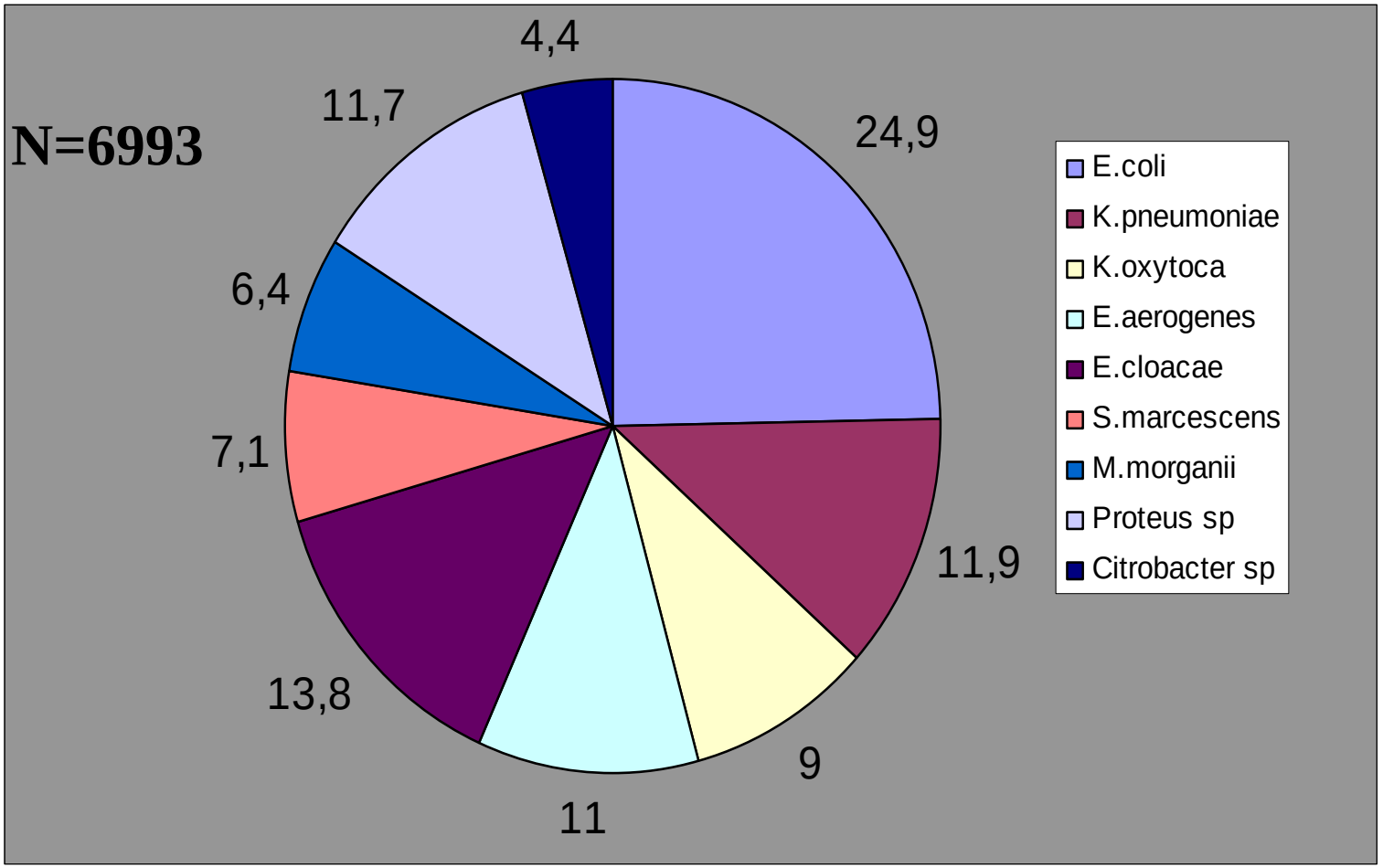
Simulations discussed for:

- 3rd generation ceph: Ceftazidime
  Cefotaxime
  4th generation ceph: Cefepime
- Carbapenems: Meropenem
  Imipenem
- Beta-lactam antibiotic:
  Piperacillin/Tazobactam
- Fluoroquinolone: Ciprofloxacine
- Aminoglycoside: Amikacine
- Tigecycline

EUCAST breakpoints on epidemiology of MYSTIC Gram negatives?

- Longitudinal surveillance study
- Initiated in 1997 (1998 in Belgium)
- Multicentre, 8 leading teaching hospitals, monitors clinical isolates collected from centres that extensively prescribe antibiotics
- Meropenem used in all participating centres
- A range of clinical units included (intensive care, onco-hematology, cystic fibrosis, general)
- Gram-positive and Gram-negative aerobes tested except for instrinsically meropenem-resistant species

Enterobacteriaceae isolated between 1998-2007 in MYSTIC surveillance



Enterobacteriaceae: What happens if EUCAST breakpoints are applied ? (n=6993)

Antibiotic	CLSI MIC breakpoints (µg/ml)			Susc. rates %	EUCAST breakpoints (µg/ml)			Susc. rates %
	S ≤	I	R ≥		S ≤	I	R ≥	
Meropenem	4	8	16	99.6	**2**	4-8	16	99.1
Ceftazidime- Cefepime	8	16	32	83.8 96.9	**1**		**16**	**75.5 *** **88.0 ***
Piperacillin- Tazobactam	16	32-64	128	84.1	**8**		**32**	**78.4 ***
Ciprofloxacin	1	2	4	83.1	0.5		**2**	**80.2 ***

* $P < 0.0001$

European MYSTIC data for Enterobacteriaceae (n=33183)

Antibiotic	CLSI MIC breakpoints Susc. (µg/ml)			rates %	EUCAST MIC breakpoints Susc (µg/ml)			rates %
	S ≤	I	R ≥		S ≤	I	R ≥	
Meropenem	4	8	16	99.5	2	4-8	16	99.2
Ceftazidime	8	16	32	83.1	1		16	**74.0**
Cefepime	8	16	32	92.0	1		16	**82.1**
Pip/Taz*	16	32-64	128	83.2	8		16	**77.8**
Cipro*	1	2	4	83.0	0.5		2	**79.6**

*¨Pip/taz: piperacillin+tazobactam

Cipro: ciprofloxacin

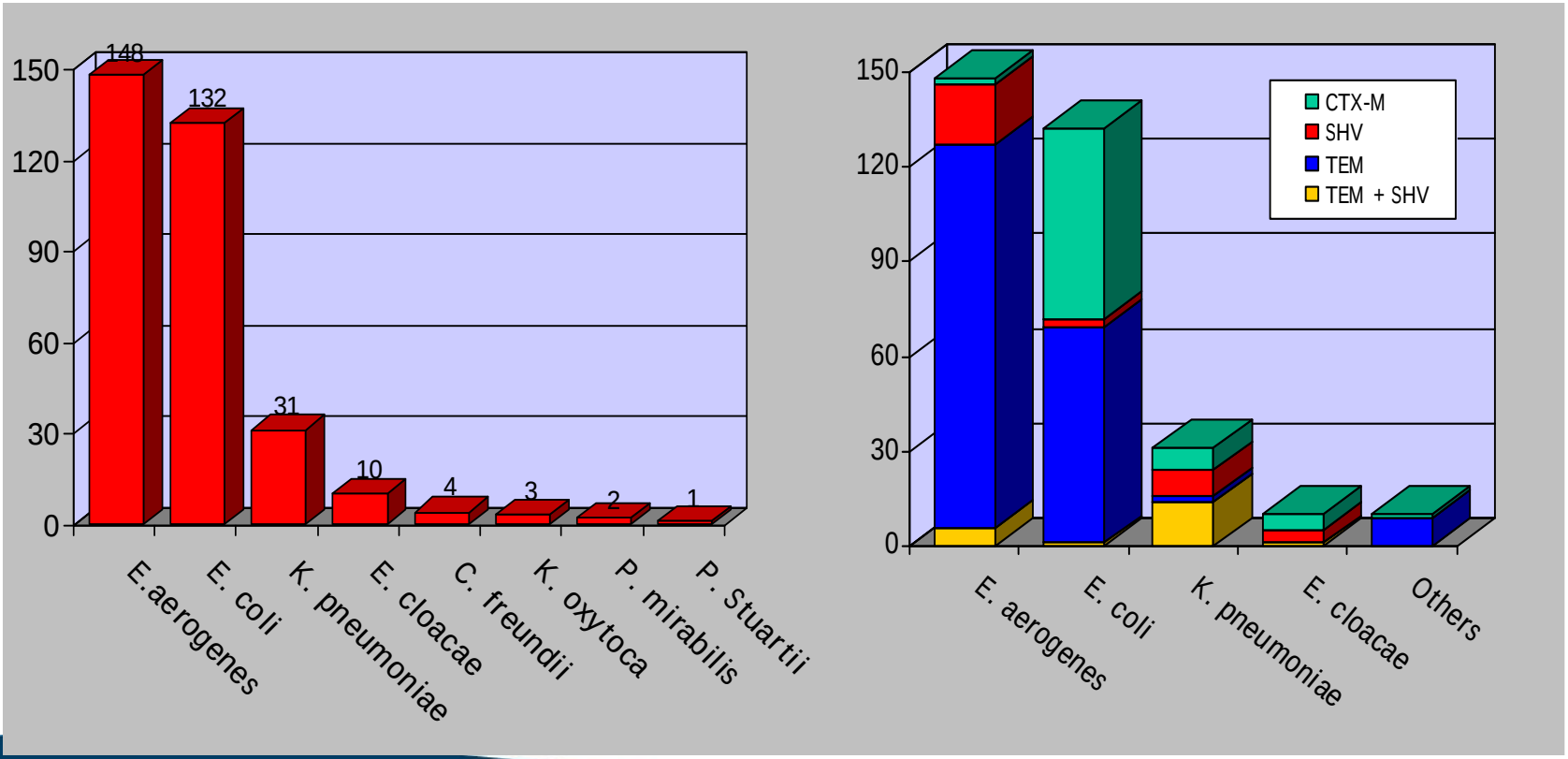
In vitro activity of 331 ESBL producing Enterobacteriaceae in 86 Belgian hospitals

- specimen: urine (50%), lower respiratory tract (25%), wounds (19%), others (6%)
- nosocomial or community-acquired
- *E. aerogenes* (44%), *E. coli* (39%), *Klebsiella pneumoniae* (13%)

Y. Glupszynski et al., ESCMID 2007, P 1355

Species and type distribution of the ESBL-producing isolates

Five consecutive +ESBLs obtained in 2006 from 86 Belgian hospitals (N=331 ESBL+ Enterobacteriaceae)
ESBL characterisation by Mplex PCR for SHV, TEM, CTX-M types



Glupczynski Y et al, ECCMID 2007, P1355

EUCAST and CLSI breakpoints for intraveously used cephalosporins

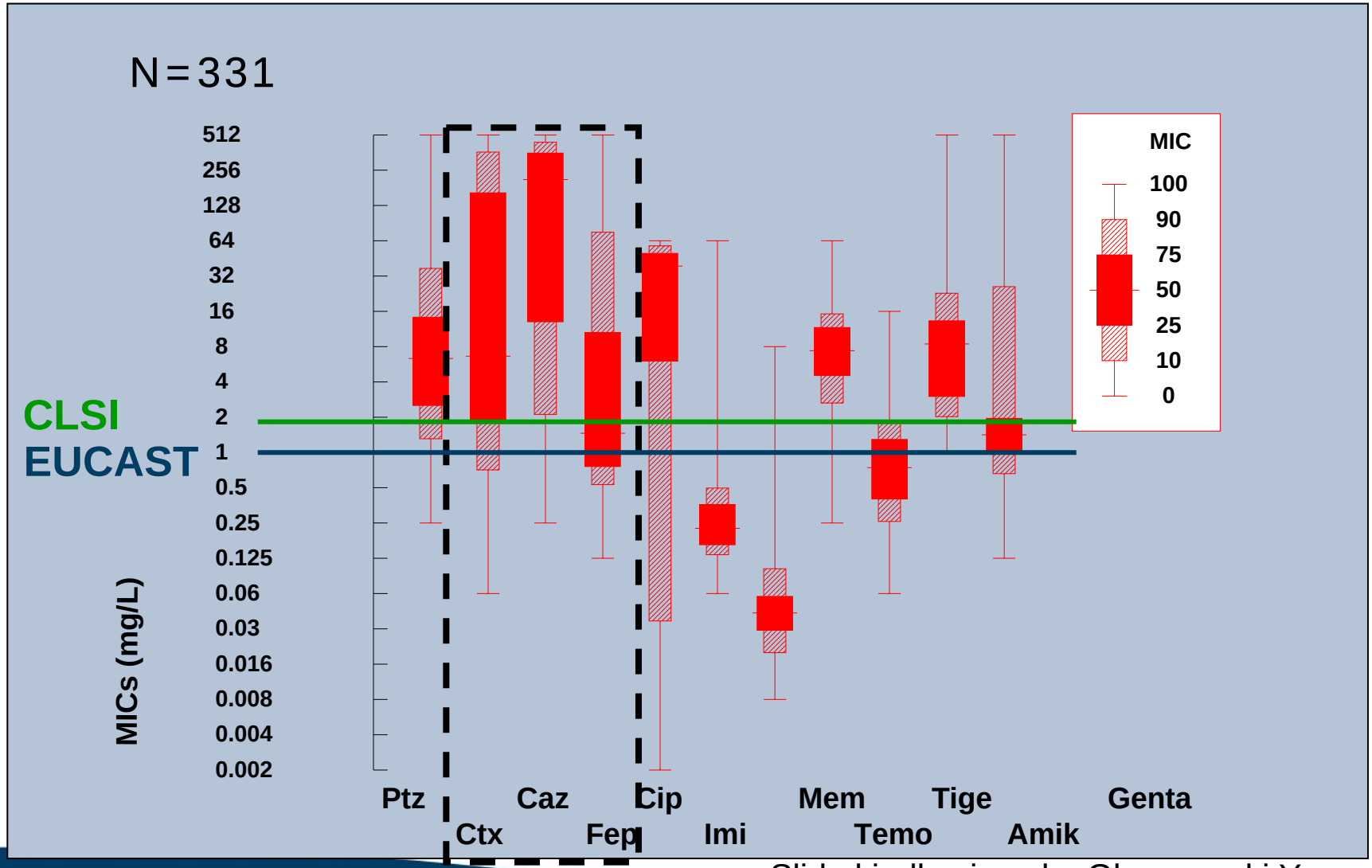
- CLSI breakpoints fail to detect many or most extended spectrum ESBLs in Enterobacteriaceae
- There is increasing evidence from clinical data and from PK/PD models that success of 3rd or 4th generation cephalosporins is related to the MIC rather than to presence or absence of an ESBL
- Breakpoints must be lower than previously recommended

E. aerogenes: What happens if EUCAST breakpoints are applied ? (n=766)

Antibiotic	CLSI MIC breakpoints (µg/ml) S ≤	I	R ≥	Susc. rates %	EUCAST breakpoints (µg/ml) S ≤	I	R ≥	Susc. rates %
Meropenem	4	8	16	96.3	**2**	4-8	16	94.2
Ceftazidime-Cefepime	8	16	32	33.7 94.0	**1**		**16**	**22.0 *** **77.4 ***
Piperacillin-Tazobactam	16	32-64	128	54.1	**8**		**32**	**32.4***
Ciprofloxacin	1	2	4	38.0	0.5		**2**	34.1

* $P < 0.0001$

MIC distributions of ESBLs-producing *Enterobacteriaceae* in Belgian hospitals



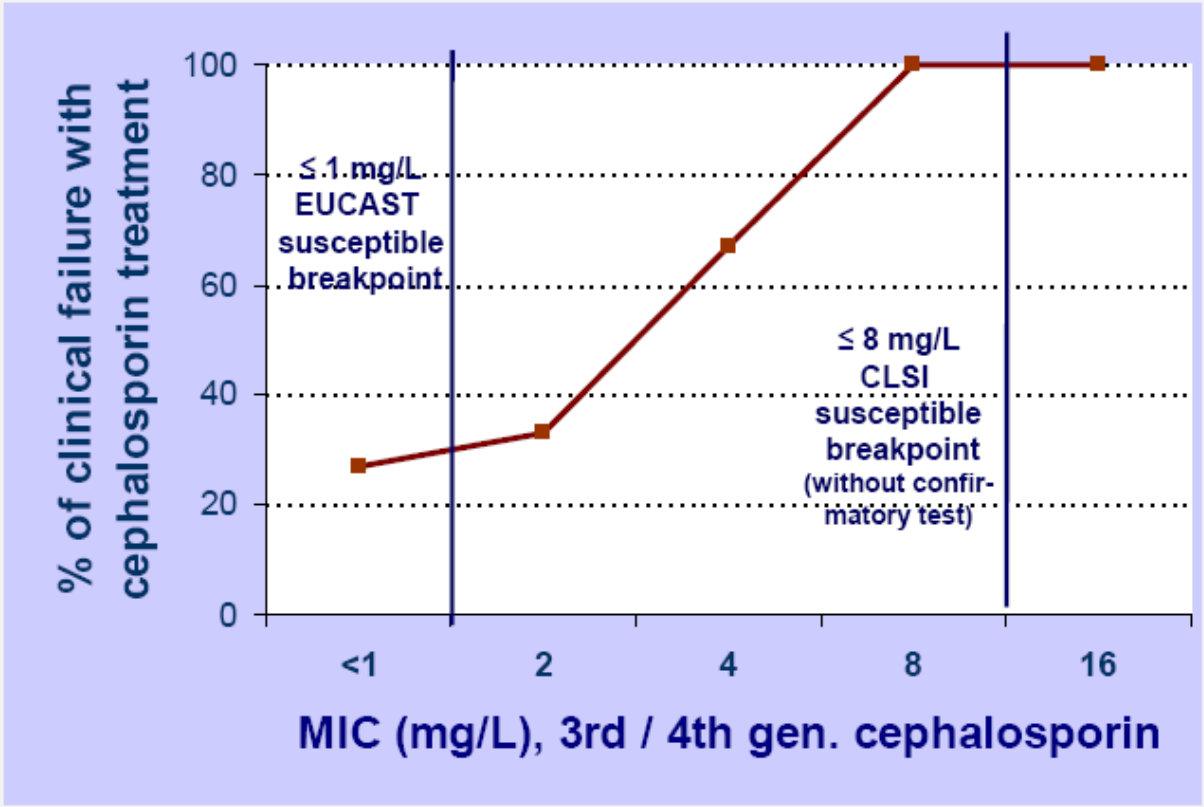
Slide kindly given by Glupczynski Y

Outcome of treatment with a broad-spectrum cephalosporin in severe infections according to the MIC value of the ESBL-producing isolate

MIC (µg/ml)	Treatment failure at 72h	30-day mortality
1	0/2 (O)	0/2 (O)
2	1/4 (25)	1/4 (25)
4	NC	NC
8	2/2 (100)	1/2 (50)
16	4/6 (66.7)	3/6 (50
32	8/11 (72.7)	3/11 (27.3)

Kang, AAC 2004

Clinical outcome of 3er/4th gen. cephalosporins treatment in patients with serious infections due to ESBL-organisms



Paterson et al. J Clin Microbiol 2001; 39:2206-12

Table 2. Comparative activity of 11 antimicrobials against 331 ESBL-producing *Enterobacteriaceae* isolates

	In (mg/L)				
Compound	**Range of MICs**	**MIC_{50}**	**MIC_{90}**	**% S CLSI Breakpoint**	**%S Eucast Breakpoint**
Piperacillin/tazobactam	0.5->256	8	64	78.5	**57.1**
Cefotaxime	0.125->256	8	>256	52.8 (14.8)*	14.8
Ceftazidime	0.5->256	256	>256	20.5 (3.3)*	3.3
Cefepime	0.25->256	2	128	72.2	**36.9**
Temocillin	0.5–64	8	16	NA	NA
Imipenem	0.125->32	0.25	0.5	98.8	98.5
Meropenem	0.016–8	0.06	0.125	99.4	99.1
Ertapenem	0.008->32	0.25	1	97.9	89.4
Ciprofloxacin	0.004->32	>32	>32	22.1	19.6
Tigecycline	0.125–16	1	2	99.4**	63.1
Amikacin	2->256	16	32	85.2	**47.1**
Gentamicin	0.25->256	2	32	85.2	76.7

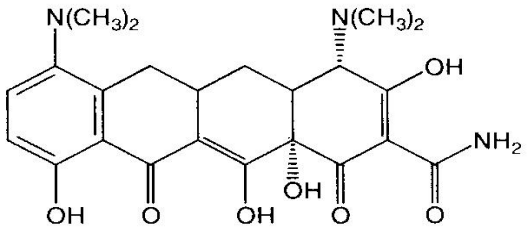
•% S for ESBL producing isolates at threshold value for screening

** No formal CSLI breakpoints for tigecycline (FDA established values)

Slide kindly given by Glupczynski Y

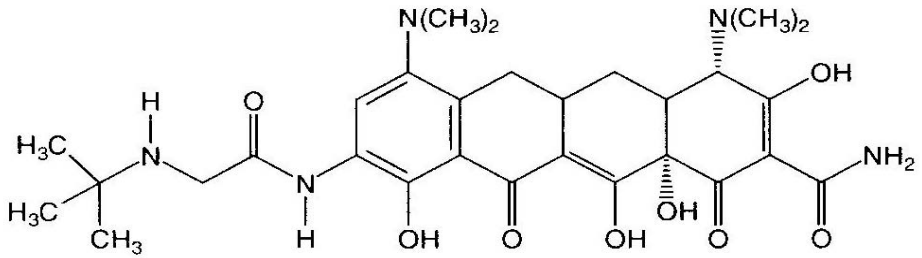
Tigecycline

- Belongs to the glycylclines



Minocycline

- Derived from minocycline by addition of a tert-butyl-glycylamido side chain on C_9 of the D-ring



Tigecycline
(GAR-936)

- Approved by FDA for clinical use in june 05

EUCAST in vitro breakpoint (µg/ml) for tigecycline

	S	I	R
non-species specific	≤0.25	0.5	>0.5
enterobacteriaceae	≤1	2	>2
Staphylococcus spp	≤0.5		>0.5
Streptococcus spp	≤0.25	0.5	>0.5
Enterococcus spp	≤0.25	0.5	>0.5

Clin Microb Infect 2006, 12: 1147

In vitro-activity of Tigecycline against aerobic Gram negatives

	tetracycline		tigecycline	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Citrobacter freundii (β-lact pos)	2	8	0.5	**2**
Enterobacter aerogenes	1	4	0.5	1
Enterobacter cloacae	2	>8	0.5	**4**
Escherichia coli	1	>8	0.25	0.5
Klebsiella pneumoniae	1	4	0.25	1
Salmonella spp	2	32	0.5	0.5
Serratia marcescens	>8	>8	2	**2**
Shigella spp.	32	32	0.25	0.5
Yersinia enterocolitica	1	2	0.25	0.5

Drugs 2004, 64, 63

In vitro activity of tigecycline isolates UZ Gasthuisberg (2007)

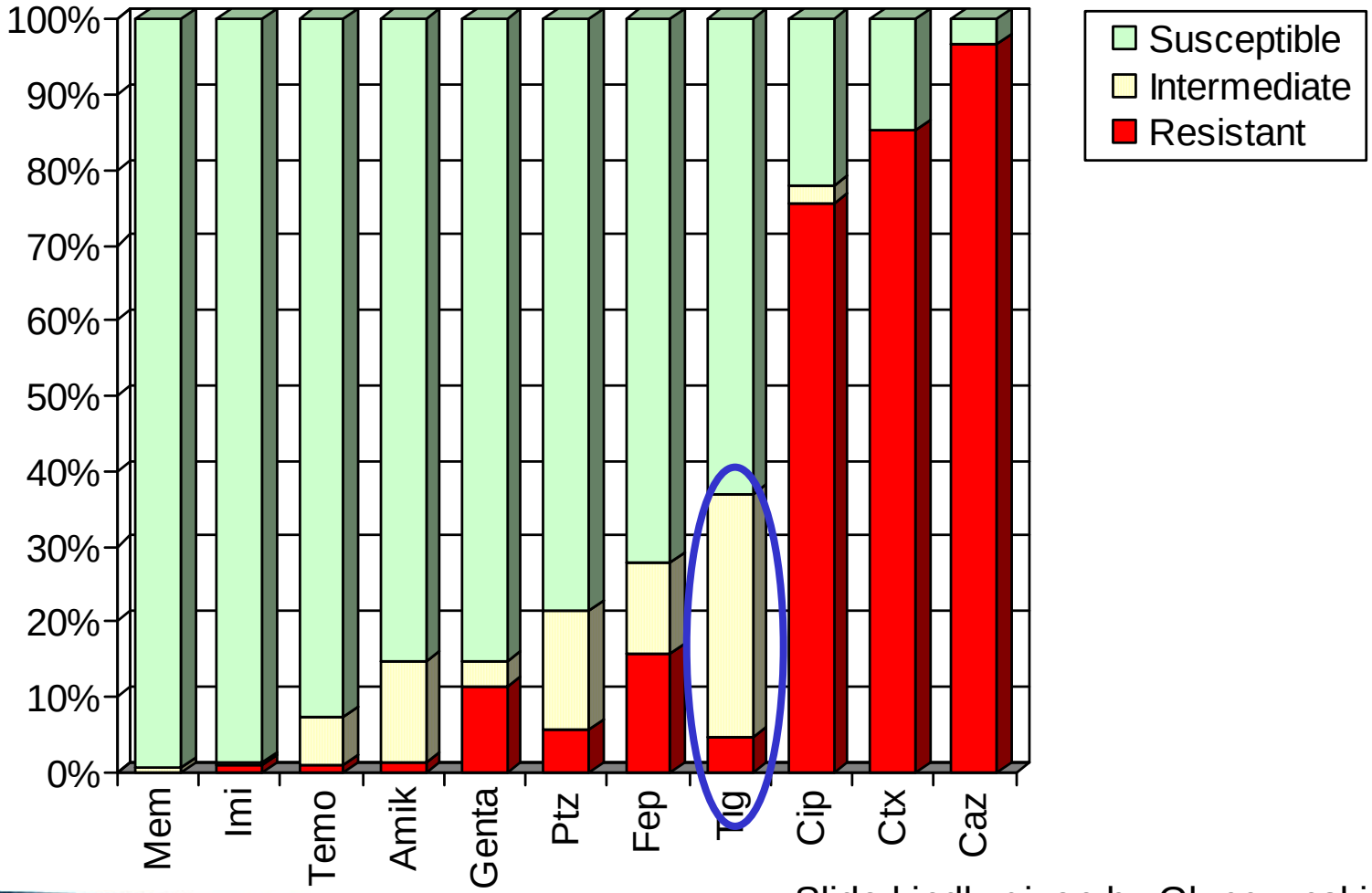
micro-organism	range	MIC_{50}	MIC_{90}
Enterobacter aerogenes (11)	0.06-4	0.5	**2**
Enterobacter cloacae (8)	0.25-4	0.5	**4**
Escherichia coli (25)	0.06-2	0.25	1
Klebsiella pneumoniae (14)	0.25-8	1	**4**
Klebsiella oxytoca (7)	0.12-1	0.5	2
Serratia spp (10)	0.25-2	0.5	1
Haemophilus influenzae (6)	0.03-2	0.25	**2**

Data kindly provided by J Verhaegen

In vitro-activity of Tigecycline against aerobic Gram negatives in UZA

	MIC_{50}	MIC_{90}	%S EUCAST	%S FDA
Enterobacteriaceae (107)	**2**	**4**	**32**	**70**
Citrobacter spp (6)	2	4	25	75
E. aerogenes (11)	2	**2**	**36**	**91**
E. cloacae (22)	2	**4**	**18**	**86**
E. coli (14)	0.5	1	100	**100**
K. oxytoca (7)	1	**4**	**57**	**71**
K. pneumoniae (11)	2	**2**	**45**	**91**
M. morganii (8)	4	16	0	38
P. mirabilis (10)	2	4	0	60
Prov. rettgeri (5)	8	8	0	0
Prov. stuartii (2)	2	4	0	50
S. marcescens (9)	4	4	0	11

Susceptibility categorization of 331 ESBL-producing *Enterobacteriacaeae* to 11 antimicrobials by Etest MIC determination



Slide kindly given by Glupczynski Y

Comparative activity of 11 antimicrobials against 132 ESBL-producing *E.coli isolates*

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Compound	In (mg/L) Range of MICs	MIC_{50}	MIC_{90}	% susceptible	Breakpoint value♦ (mg/L)
Piperacillin/tazobactam	0.25->256	2	32	85.6	16
Cefotaxime	0.06->256	256	>256	10.6	1*
Ceftazidime	0.5->256	16	>256	11.4	1*
Cefepime	0.25->256	16	256	45.5 (22)	8 (1*)
Temocillin	0.5–32	8	16	93.2	16
Imipenem	0.125-0.5	0.25	0.25	100	4
Meropenem	0.008–0.25	0.03	0.06	100	4
Ciprofloxacin	0.004->32	>32	>32	36.4 (22.8)♣	1
Tigecycline	0.125–2	0.5	1	**98.5**	1
Amikacin	1->256	4	16	82.6	16
Gentamicin	0. 5->256	1	64	79.5	4

♦ CLSI breakpoint values except when otherwise stated
* EUCAST clinical breakpoint values for extended-spectrum cephalosporins
♣ Susceptibility rates after inclusion of isolates displaying low level resistance to ciprofloxacin

Slide kindly given by Glupczynski Y

Comparative activity of 11 antimicrobials against 148 ESBL-producing *Enterobacter aerogenes* isolates

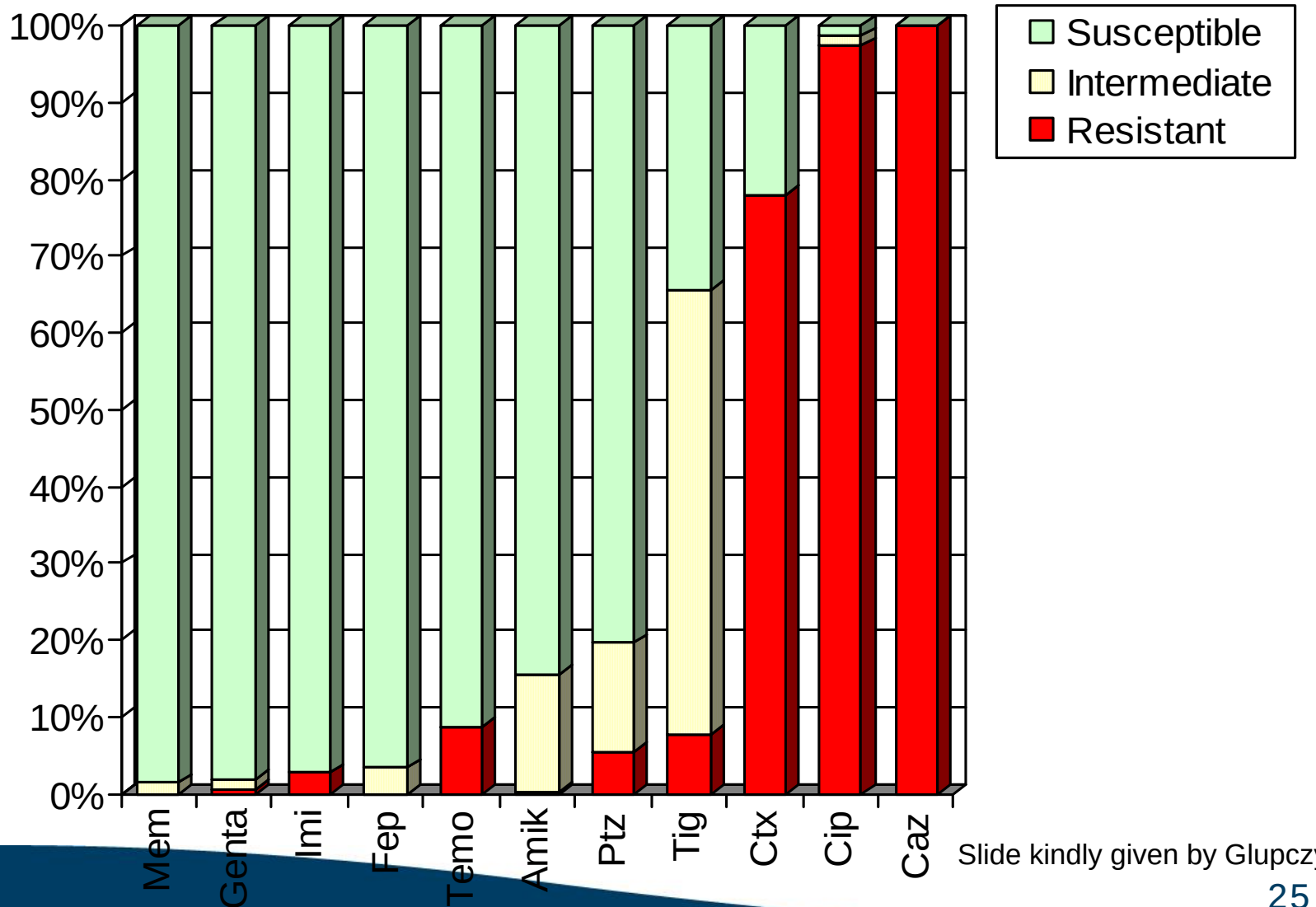
	In (mg/L)				
Compound	**Range of MICs**	**MIC_{50}**	**MIC_{90}**	**% susceptible**	**Breakpoint value♦ (mg/L)**
Piperacillin/tazobactam	1-64	16	32	80.4	16
Cefotaxime	0.25-128	4	16	22.3	1*
Ceftazidime	16->256	>256	>256	0	1*
Cefepime	0.25-16	1	2	96.6 (66.9)	8 (1*)
Temocillin	2-64	16	16	91.2	16
Imipenem	0.25-64	0.5	1	97.3	4
Meropenem	0.016–8	0.06	0.125	98.6	4
Ciprofloxacin	0.125-64	>32	>32	1.4	1
Tigecycline	0.25–4	2	2	**36.5**	1
Amikacin	2->256	16	32	84.5	16
Gentamicin	0.25-32	2	4	98.0	4

♦ CLSI breakpoint values except when otherwise stated

* EUCAST clinical breakpoint values for extended-spectrum cephalosporins

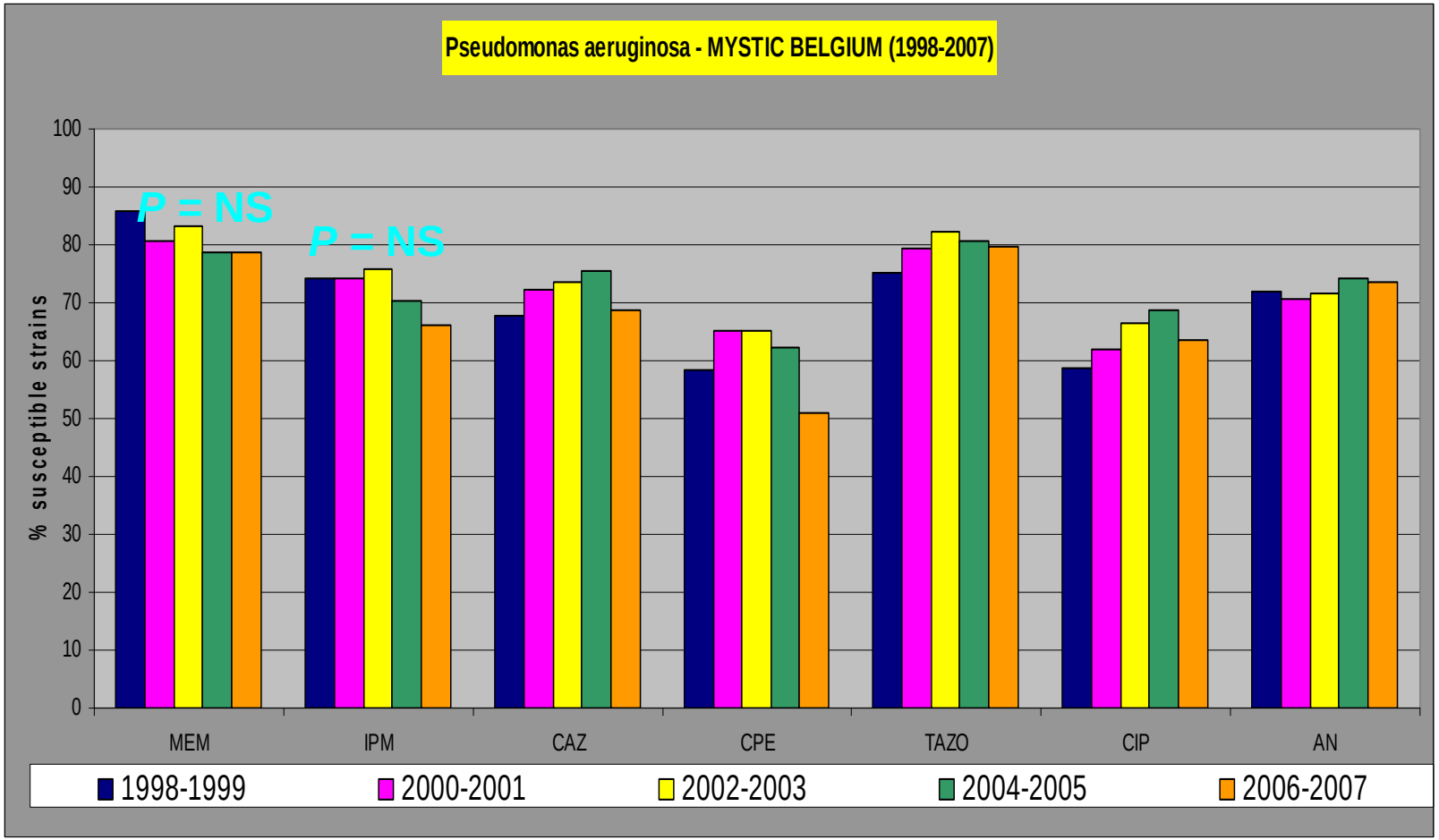
Slide kindly given by Glupczynski Y

Susceptibility categorization of 148 ESBL-producing *E.aerogenes* to 11 antimicrobials by Etest MIC determination



Slide kindly given by Glupczynski Y

Trends in Susceptibility of *P.aeruginosa* to Meropenem and Comparator Agents (n=2409)



P. aeruginosa : What happens if EUCAST breakpoints are applied(n=2409)

Antibiotic	CLSI MIC breakpoints (µg/ml)			Susc. rates %	EUCAST MIC breakpoints (µg/ml)			Susc. rates %
	S ≤	I	R ≥		S ≤	I	R ≥	
Meropenem	4		16	81.6/14.7	**2**		16	**75.2 ***/14.7
Ceftazidime-Cefepime	8		32	72.3/21.8 61.2/25.8	8		**16**	72.3/**27.7** 61.2/**38.8**
Piperacillin-Tazobactam	64		128	80.4/19.6	**16**		**32**	**69.3 */30.7**
Ciprofloxacin	1		4	64.1/27.7	0.5		2	56.7/35.8

* $P < 0.0001$

European MYSTIC data for *Pseudomonas aeruginosa* (n=12170)

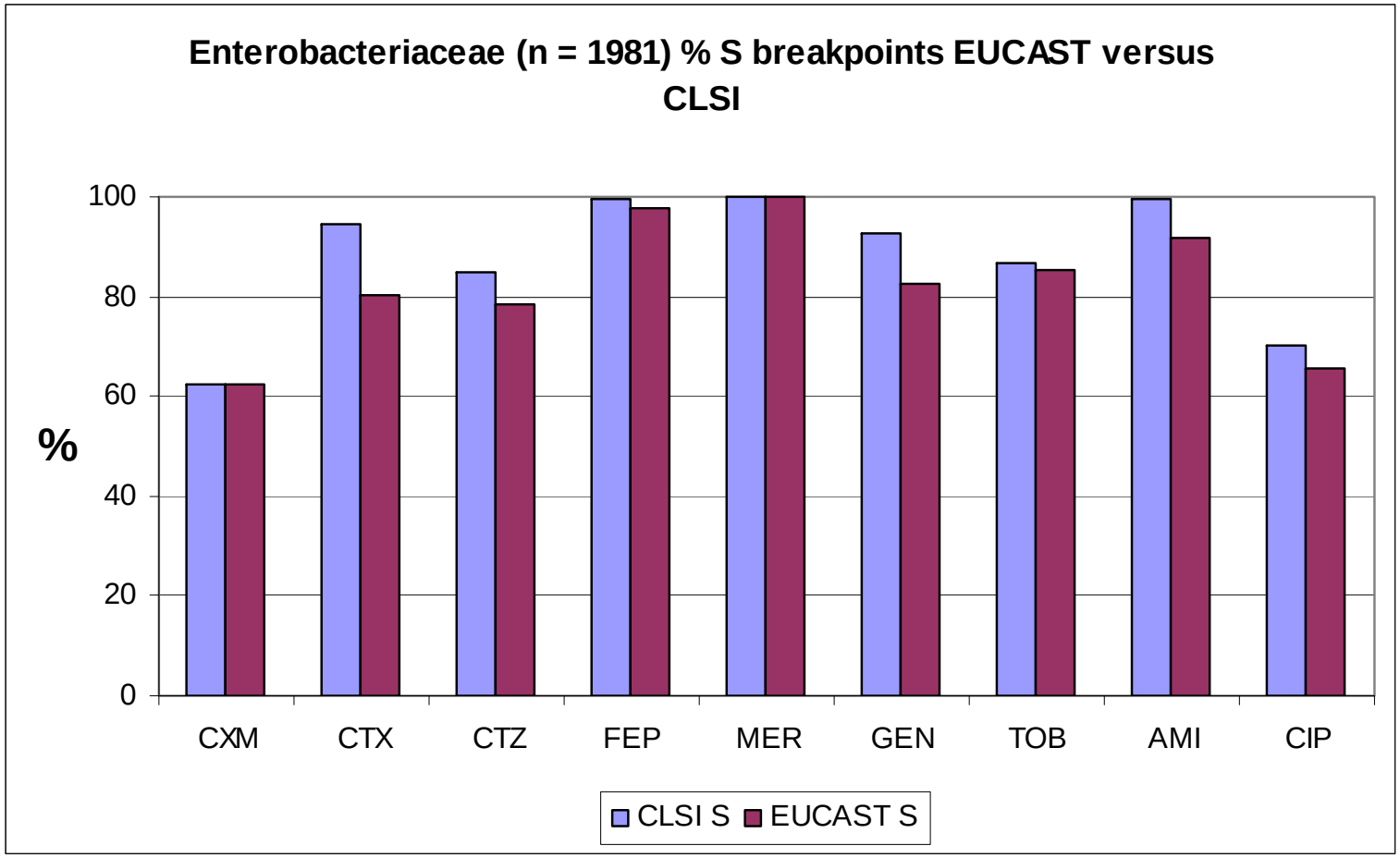
Antibiotic	CLSI MIC breakpoints (µg/ml)		Susc. rates %	EUCAST MIC breakpoints (µg/ml)		Susc. rates %
	S ≤	R ≥		S ≤	R ≥	
Meropenem	4	16	77.1	2	16	**69.6**
Ceftazidime	8	32	71.2	8	16	71.2
Cefepime	8	32	60.3	8	16	60.3
Pip/Taz*	64	128	81.3	16	32	**66.4**
Cipro*	1	4	64.6	0.5	2	55.7

*¨Pip/taz: piperacillin+tazobactam

Cipro: ciprofloxacin

Are individual local data important?

Enterobacteriaceae (n = 1981) from non University hospital (1000 beds): % S breakpoints EUCAST versus CLSI



Enterobacteriaceae (n = 1981)
% S breakpoints EUCAST versus CLSI

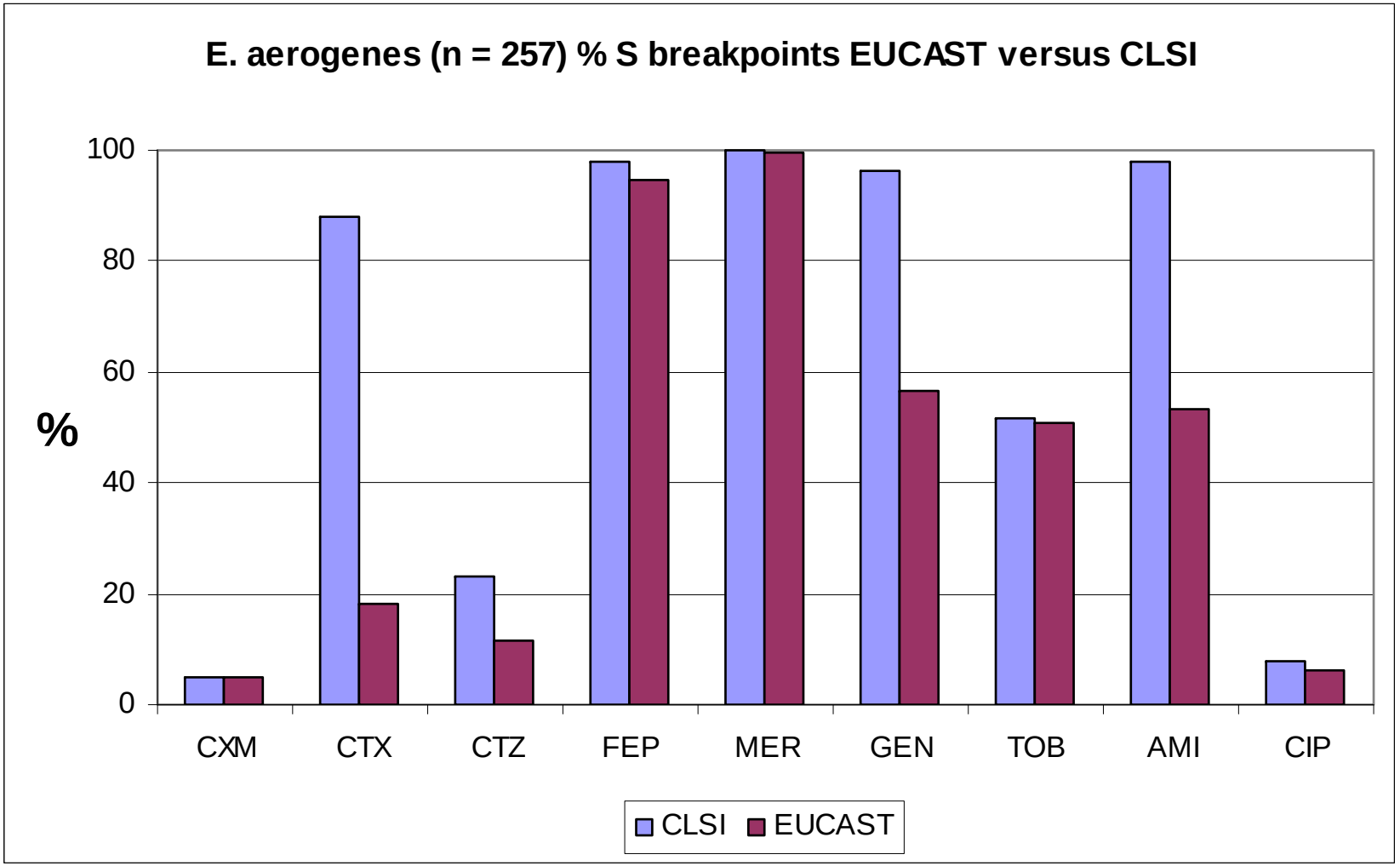
Enterobacteriaceae

	CXM	CTX	CTZ	FEP	MER	GEN	TOB	AMI	CIP
CLSI S	62.41	94.6	85	99.5	99.9	92.4	86.5	99.4	70.1
EUCAST S	62.41	80.3	78.5	97.5	99.9	82.7	85.5	91.7	65.8

	CXM	CTX	CTZ	FEP	MER	GEN	TOB	AMI	CIP
% Verschil S	0	14.3	6.47	2.02	0.05	9.71	1.08	7.65	4.33

*: NS

E. aerogenes (n = 257) from non University hospital (1000 beds): % S breakpoints EUCAST versus CLSI



Enterobacter aerogenes (n = 257)
% S breakpoints EUCAST versus CLSI

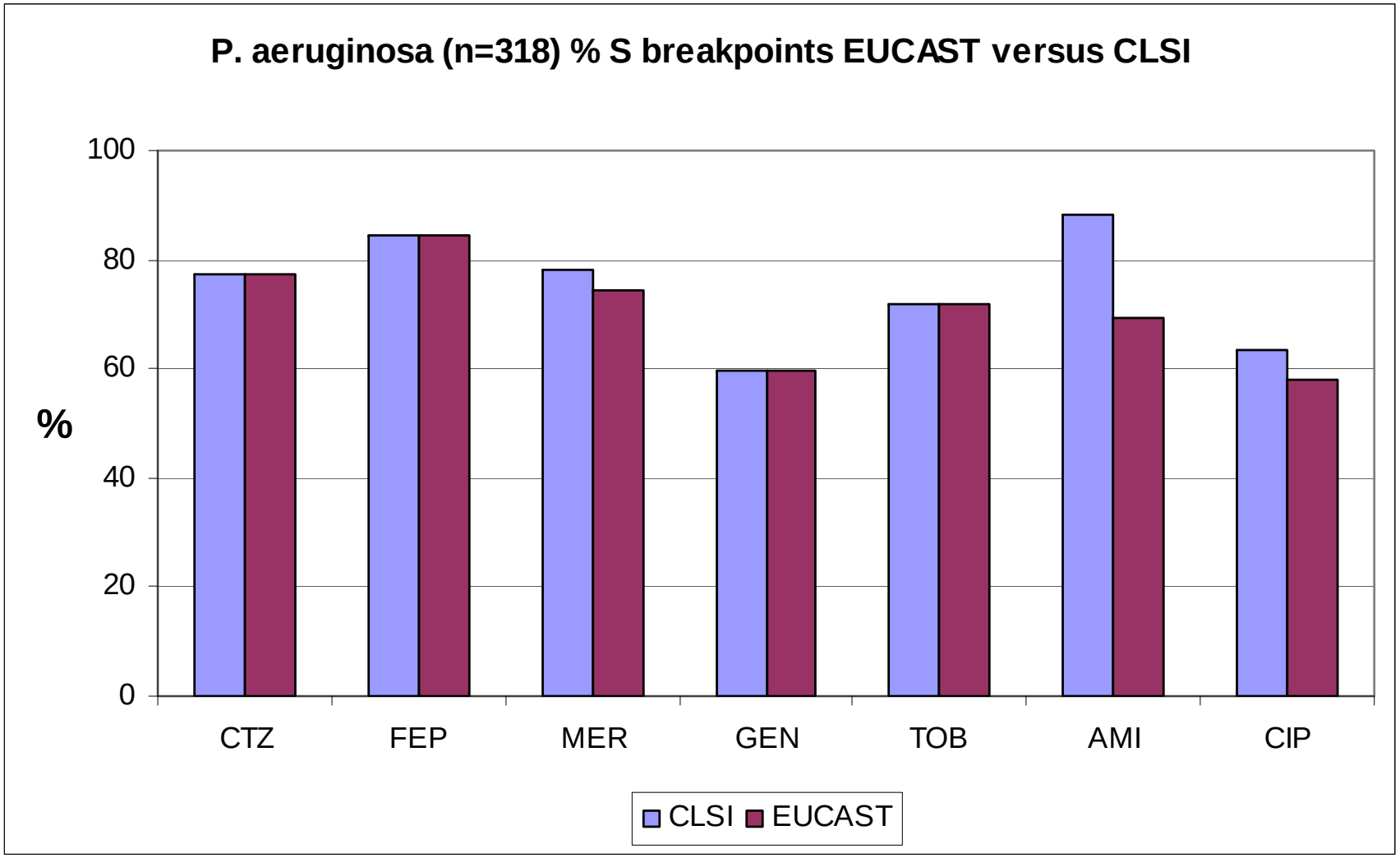
Enterobacter aerogenes

	CXM	CTX	CTZ	FEP	MER	GEN	TOB	AMI	CIP
CLSI S	5.06	87.9	23	98.1	100	96.5	51.8	98.1	7.78
EUCAST S	5.06	18.3	11.7	94.6	99.6	56.6	51	53.3	6.23

	CXM	CTX	CTZ	FEP	MER	GEN	TOB	AMI	CIP
% Verschil S	0	69.6	11.3	3.5*	0.39	39.8	0.78	44.7	1.56*

*: NS

P. aeruginosa (n = 318) from non University hospital (1000 beds): % S breakpoints EUCAST versus CLSI



P. aeruginosa (n= 318) % S breakpoints EUCAST versus CLSI

P. aeruginosa

	CTZ	FEP	MER	GEN	TOB	AMI	CIP
CLSI S	77.36	84.59	78.30	59.75	71.70	88.36	63.52
EUCAST S	77.36	84.59	74.53	59.75	71.70	69.18	57.86

	CTZ	FEP	MER	GEN	TOB	AMI	CIP
% Verschil S	0.00	0.00	3.77 *	0.00	0.00	19.18	5.66 *

* : NS

Epidemiological consequences of new breakpoints: CONCLUSIONS

When implementing EUCAST breakpoints:

- **New cephalosporin breakpoints for Enterobacteriacaeae decrease the risk to report false susceptibilities in ESBLs.**
- **An important decrease in cefepime activity against ESBL- producing pathogens is observed.**
- **Carbapenem activity against enterobacteriaceae, including ESBL-producing Enterobacteriaceae does not change.**
- **Whereas >98% of ESBL- producing *E.coli* remain susceptible for Tigecycline, % of susceptibility among *Enterobacter* spp and *Klebsiella* spp isolates is decreased: < 50% are susceptible.**

Epidemiological consequences of new breakpoints: CONCLUSIONS

When implementing EUCAST breakpoints:

- **Susceptibility rates for ceftazidime and cefepime in *P. aeruginosa* are not affected.**
- **Although susceptibility rates decrease, meropenem remain the most active agents against *P. aeruginosa* the activity of Pip/tazo is affected more.**
- **Variability is observed between local, national and international consequences of implementing EUCAST breakpoints underlying the importance of surveillance studies at all levels to optimise therapy and limit resistance spread.**