



Mogliano Veneto (TV), 28 Marzo 2014



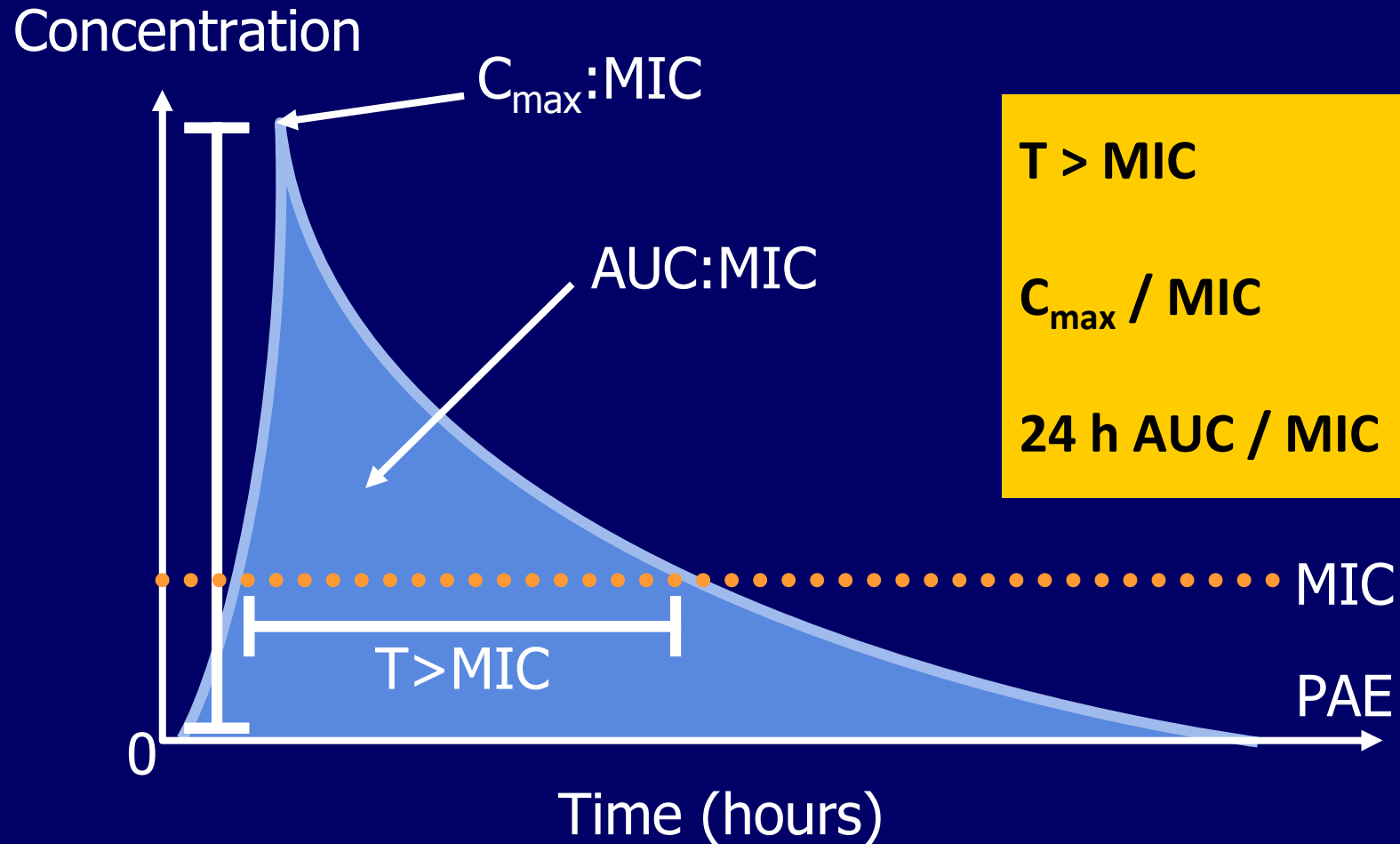
**FOCUS ON ANTIMICROBIAL RESISTANCE AND ANTIMICROBIAL
SUSCEPTIBILITY TESTS: IN MEMORY OF PROF. MARCO TONI**

Epidemiologia delle resistenze nei batteri Gram negativi

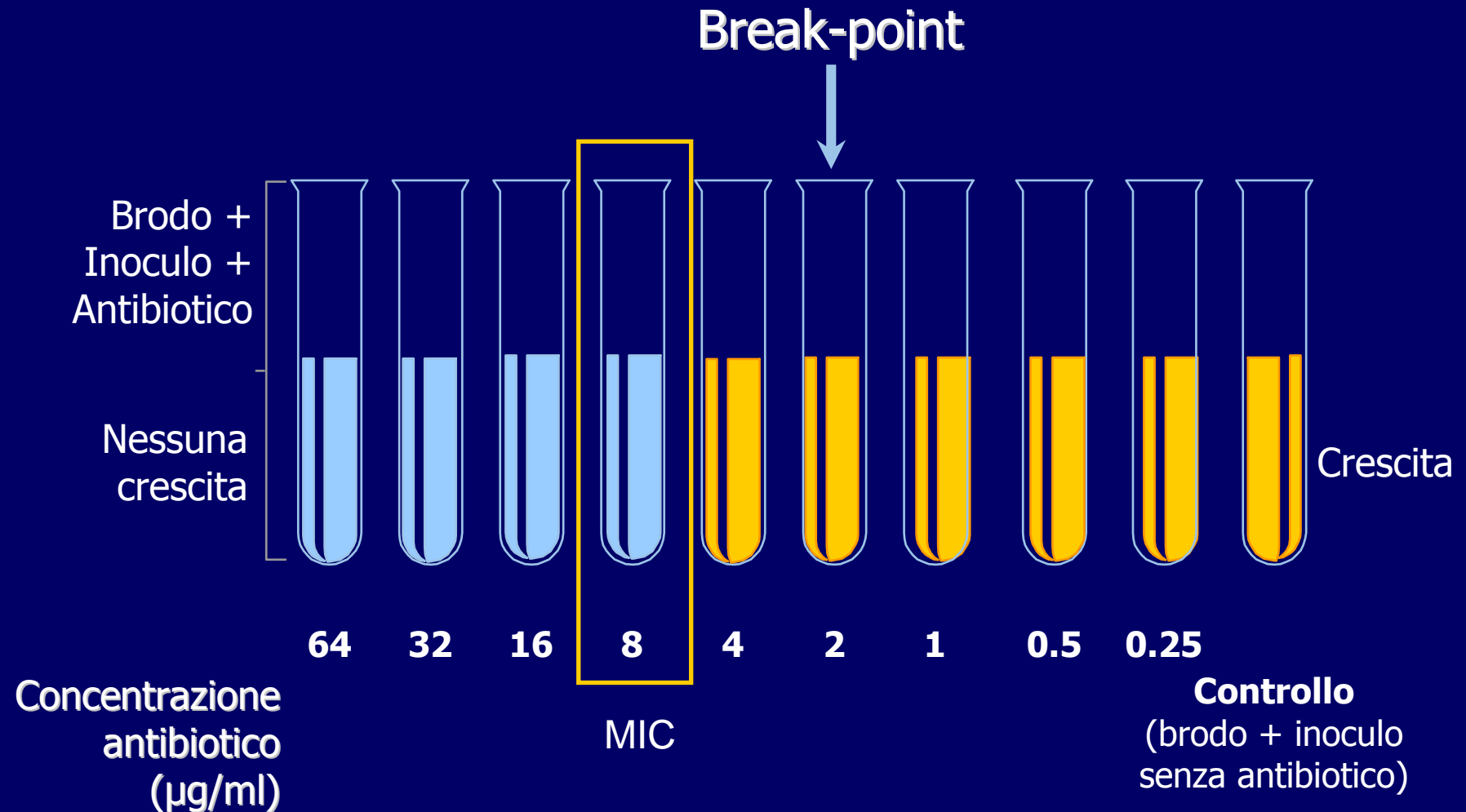
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Considerations for Successful Antimicrobial Therapy

PK/PD parameters affecting antibiotic efficacy *in vivo*



Test in Microdiluzione (MIC)



SENSITITRE CUSTOM PLATE FORMAT

EUCAST BREAKPOINTS SYSTEM

ITGN4F - GRAM NEGATIVE

N.	Sign	Drug	Wild Type	Clinical breakpoint		Range dilutions	
				S ≤	R >	From	To
1	P/T4	Piperacillin-tazobactam	2 - 8 - 16	8 / 16	16	1	128
2	AUG2	Amoxicillin/clavulanate	2 - 8		8	1	8
3	TAZ	Ceftazidime	0,125 - 0,25 - 0,5 - 1 - 2 - 8	1 / 8	4 / 8	0,125	128
4	FOT	Cefotaxime	0,064 - 0,125 - 0,25 - 0,5	1	2	0,064	32
5	CIP	Ciprofloxacin	0,032 - 0,125 - 1	0,5 / 1	1	0,032	2
6	LEVO	Levofloxacin	0,125 - 0,25 - 0,5	1	2	0,125	4
7	AMI	Amikacin	8 - 16	8	16	1	16
8	COL	Colistin	2 - 4	2 / 4	2 / 4	0,25	4
9	MERO	Meropenem	0,125 - 0,25 - 2	2	8	0,125	32
10	ETP	Ertapenem	0,064	0,5	1	0,064	2
11	TGC	Tigecycline	1 - 2 - 4 - 8 - 64	1	2	0,064	2
12	SXT	Trimethoprim / sulfamethoxazole	1	2 / 4	4	0,064	4
13	FOS	Fosfomicin	8	32	32	8	64
14	NIT	Nitrofurantoin	64	64	64	4	64

2012- MICROBIOLOGIA UDINE: *E. coli* da materiali nobili

14 marzo 2013

Selection Name: escherichia coli
 Organismo: Escherichia coli
 PlateType: ITGN4F

Materiale: Agoaspirato, Ascesso, Bile, Broncolavaggio, Cannula endotracheale, Cannula endotracheale, Catetere arterioso, Catetere venoso centrale, Emocoltura, Emocoltura pediatrica, Fluido di toracentesi, Frammenti protesi, Linfonodo, Liquido amniotico, Liquido ascitico, Liquido di drenaggio, Liquido drenaggio addominale, Liquido pericardico, Liquido peritoneale, Liquido sinoviale, Liquido, Materiale bioplastico, Materiali...

Date Range: 01/01/2012 to 31/12/2012

CIPROFLOXACINA: - MIC breakpoint: $\leq 0,5$ (S)
- MIC reale = 0.03 (S)



S

R

Breakpoint clinici

Antimicrobic	Tested	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
Amikacin	550						9.4	61.1	17.5	6.4	3.8	1.8			
Amoxicillin/ Clav.	550						2.0	16.9	22.2	20.4	38.5				
Cefotaxime	550		68.0	5.3	1.8	1.1	0.7	2.0	1.3	1.3	0.9	3.2	14.4		
Ceftazidime	550			58.9	13.3	5.6	2.5	2.9	1.3	5.3	5.3	2.7	1.1	0.9	0.2
Ciprofloxacin	550	52.6	1.5	1.6	4.2	0.7	0.5	0.7	38.2						
Colistin	550				86.7	11.6	0.2			1.5					
Ertapenem	550		97.3	1.2	0.9	0.4	0.2								
Fosfomycin + G6P	550									95.8	1.6	0.9	0.6	1.1	
Levofloxacin	550			53.7	2.9	3.6	0.9	0.5	1.3	37.1					
Meropenem	550			99.6	0.2			0.2							
Nitrofurantoin	550								24.2	36.9	28.2	7.1	2.0	1.6	
Piperacillin/ Taz.	550						53.4	18.5	8.4	6.2	5.3	2.7	1.1	2.2	2.2
Tigecycline	550		30.2	52.9	12.4	3.8	0.5	0.2							
Trimethoprim/ Sulph.	550		46.9	6.2	5.1	1.8	1.6	0.4	1.3	36.7					

Escherichia coli (da materiali nobili)

DISTRIBUZIONE MIC 2013

2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
TV	AMOXI/CLAV	848	59						2	9	23	25	41				
UD	AMOXI/CLAV	616	62						2	15	24	21	38				
TV	PIPER/TAZO	848	91						39	36	9	7	2	1	1	2	3
UD	PIPER/TAZO	612	90						46	27	12	5	2	3	2	1	2
TV	CEFOTAXIME	848	79		67	7	3	1	1	1	1	2	4	3	10		
UD	CEFOTAXIME	612	81		68	7	4	1	1	1	1	4	0	2	11		
TV	CEFTAZIDIME	848	80			54	19	5	2	4	1	6	4	3	2		
UD	CEFTAZIDIME	612	82			60	17	3	2	3	3	5	4	2	1		
TV	CIPROFLOXACINA	848	61	44	9	2	5	1	1		38						
UD	CIPROFLOXACINA	612	65	49	9	4	3	0	1		34						
TV	LEVOFLOXACINA	848	62			45	2	5	10	1	1	36					
UD	LEVOFLOXACINA	612	66			50	4	2	10	1	1	32					
2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256

Escherichia coli (da materiali nobili)

DISTRIBUZIONE MIC 2013

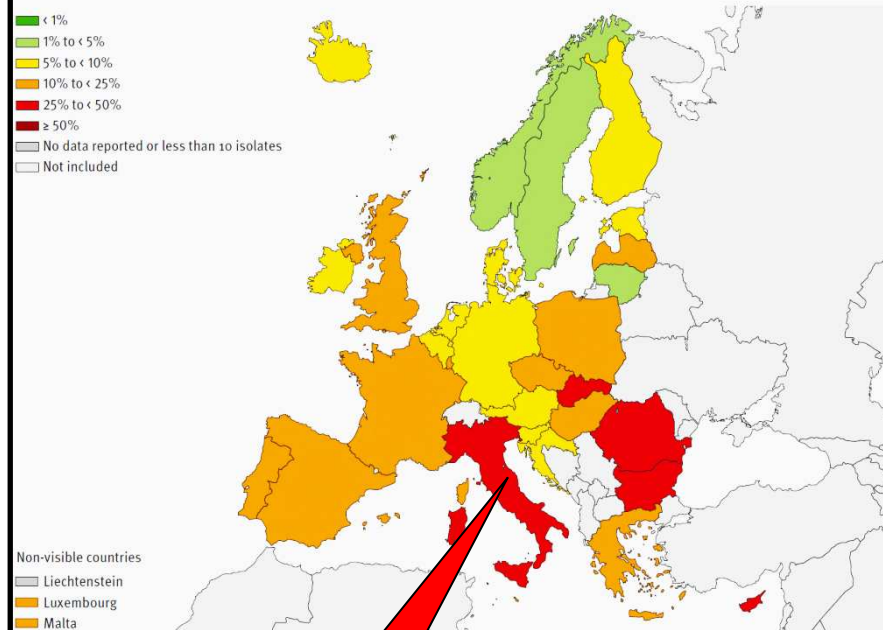
2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
TV	AMIKACINA	848	97						8	55	28	6	1	2			
UD	AMIKACINA	612	95						11	51	27	6	3	2			
TV	TRIMET/SULFA	848	64		39	8	5	10	1	1	0	36					
UD	TRIMET/SULFA	612	69		43	8	5	10	2	1	1	30					
TV	NITROFURANTOINA	848	100								19	28	32	20	1		
UD	NITROFURANTOINA	612	99								22	33	27	16	1	1	
TV	TIGECICLINA	848	100		36	52	10	1	1								
UD	TIGECICLINA	612	100		32	52	14	2									
TV	ERTAPENEM	848	100		98	2	0	0									
UD	ERTAPENEM	612	100		97	2	1	0									
TV	MEROPENEM	848	100			99	1										
UD	MEROPENEM	612	100			99	1										
TV	COLISTINA	848	99				73	25	1	0	0	1					
UD	COLISTINA	612	98				82	16	0	0	0	2					
2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256

EARS-NET 2012: % of invasive isolates with resistance to third-generation Cephalosporins

Escherichia coli

Klebsiella pneumoniae

Figure 3.1. *Escherichia coli*. Percentage (%) of invasive isolates with resistance to third-generation cephalosporins by country, EU/EEA countries, 2012



26.3%

UDINE

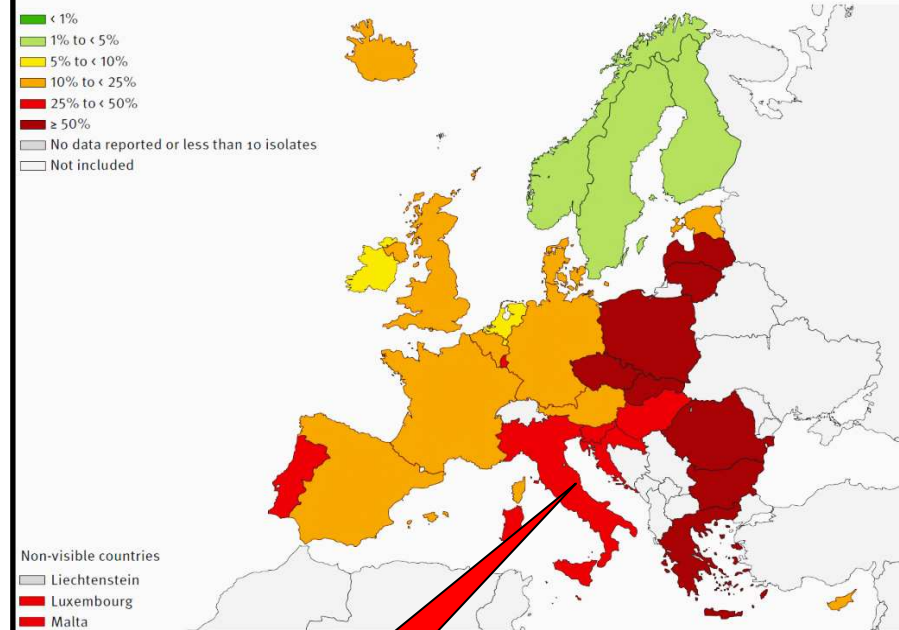
19

TREVISO

21

2013

Figure 3.10. *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with resistance to third-generation cephalosporins, by country, EU/EEA countries, 2012



47.7%

UDINE

20%

TREVISO

30%

***Escherichia coli* ESBL+ (CTX-M-1), EUCAST 2012**

MIC (mg/L)

Ampicillin	>128	R	Amikacin	2	S
Amoxi/Clav	32	R	Gentamicin	16	R
Pip/Tazo	8	S	Ciprofloxacin	> 32	R
Cephalotin	32	R	Levofloxacin	> 32	R
Cefotaxime	32	R	ESBL Positive		
Ceftazidime	1	S			
Cefepime	8	R			
Ertapenem	0.12	S			

Some ESBL-producing strains will be reported susceptible to 3rd and 4th gen. cephalosporins (mostly with ceftazidime and cefepime)

Etest per ESBL

“Ceppo produttore di beta-lattamasi a spettro esteso (ESBL); ad eccezione dei carbapenemi, la terapia con beta-lattamici (incluse cefalosporine a spettro esteso, aztreonam e combinazioni con inibitori) potrebbe risultare scarsamente efficace o inefficace anche se in vitro il ceppo appare sensibile a questi farmaci. Nel caso in cui si intendano utilizzare tali farmaci si raccomanda preventiva consulenza con un esperto di terapia antibiotica”.

+
clavulanate

**UDINE - EPIDEMIOLOGIA 2013 : % ESBL - AMP_c - CBPEN
ESPRESSE NELLE ENTEROBACTERIACEAE -
TOTALE ISOLATI ED ISOLATI DA MATERIALI NOBILI**

Specie	TOT.	MAT. NOBILI	TOT.	MAT. NOBILI	TOT.	MAT. NOBILI
	ESBL	ESBL	AMP _c	AMP _c	CBPEN	CBPEN
<i>Citrobacter spp.</i>	3,5%	2,3%	7,5%	18,2%	/	/
<i>Enterobacter aerogenes</i>	/	/	29,9%	34,1%	/	/
<i>Enterobacter cloacae</i>	1,9%	/	19,5%	18,6%	0,5%	/
<i>Escherichia coli</i>	11,9%	18,2%	0,4%	0,4%	0,1%	0,3%
<i>Klebsiella pneumoniae</i>	9,1%	7,0%	0,3%	/	5,5%	7,5%
<i>Morganella morganii</i>	2,1%	4,4%	12,5%	17,8%	/	/
<i>Proteus mirabilis</i>	3,9%	4,2%	0,6%	/	/	/
<i>Providencia stuartii</i>	56,6%	81,2%	/	/	/	/

UDINE – EPIDEMIOLOGIA 2010 - 2011 – 2012 - 2013

% ESBL - AMP_c - CBP ESPRESSE NELLE ENTEROBACTERIACEAE - TUTTI GLI ISOLATI

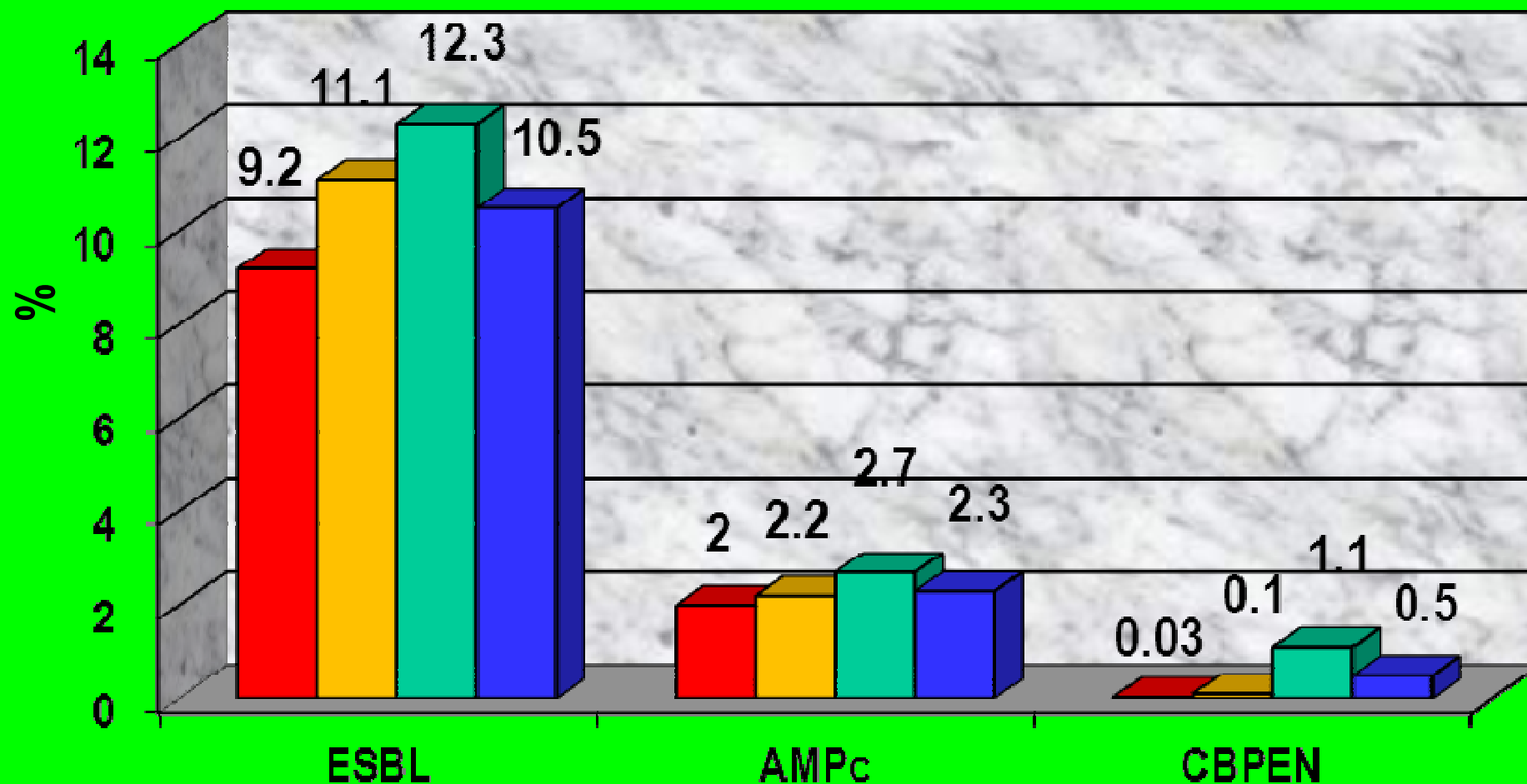
Epidemiologia
UDINE

2010

2011

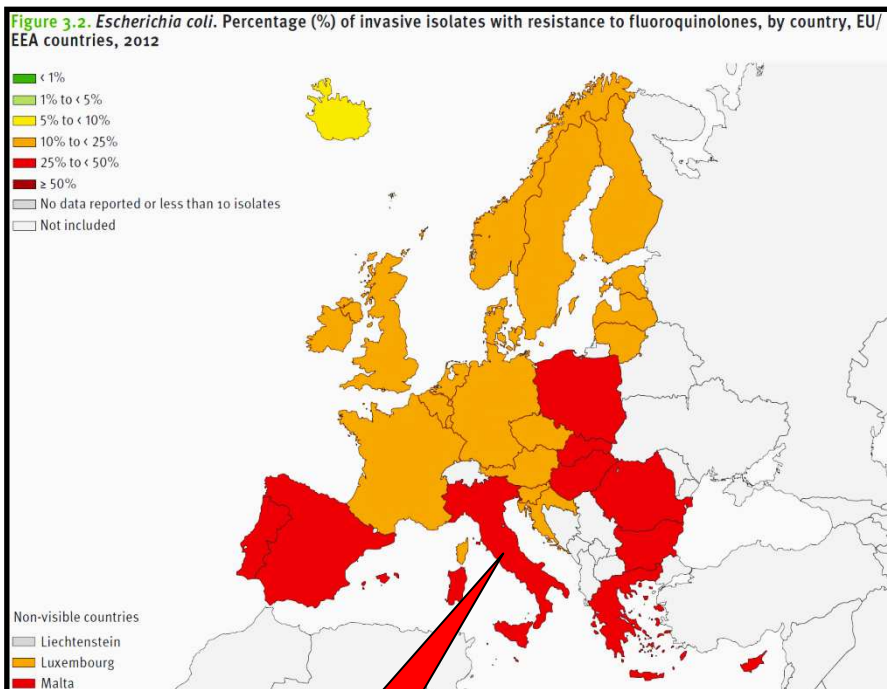
2012

2013



EARS-NET 2012: (%) of invasive isolates with resistance to Fluoroquinolones

Escherichia coli



42%

UDINE

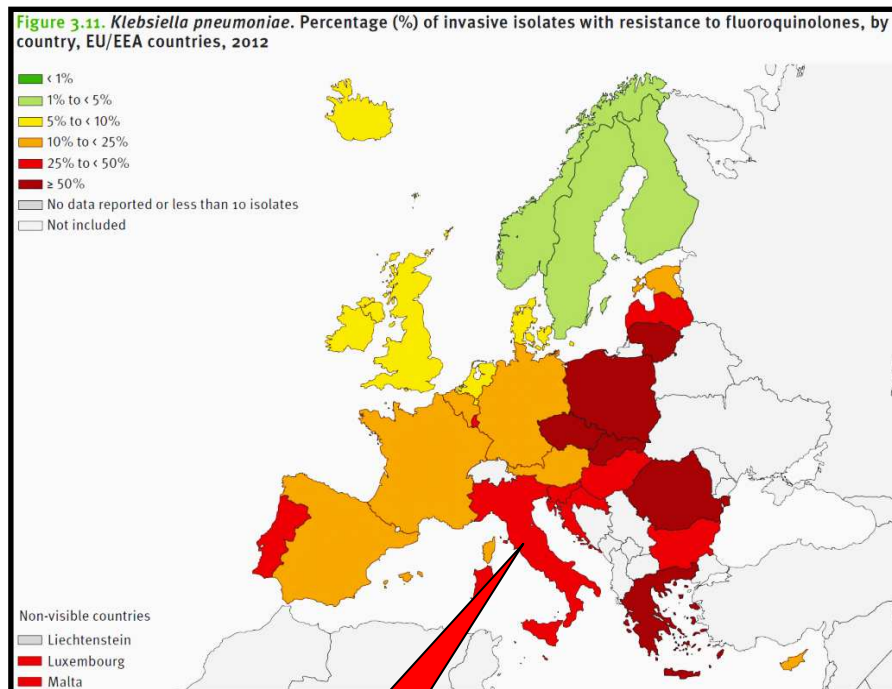
35%

TREVISO

39%

2013

Klebsiella pneumoniae



49.6%

UDINE

18%

TREVISO

30%

Bronco-alveolo lavaggio:

sviluppo di *E. coli*

Carica batterica: 10^6 UFC/ml

Farmaco	Categoria	MIC (mg/L)
Ampicillina	R	≥ 32
Amoxi/Clav.	S	8/2
Piperacillina	S	4
Pipera/Tazob.	S	4/4
Cefotaxime	S	0,5
Ceftazidime	S	0,25
Imipenem	S	0,03
Gentamicina	S	1
Ciprofloxacina	S	0,5

BRONCOALVEOLO LAVAGGIO:

<i>P. aeruginosa</i>		
Farmaco	Interpretazione	MIC (mg/L)
Ceftazidime	S	2
Ciprofloxacina	S	0,5
Gentamicina	S	4
Imipenem	S	0,5
Piperacillina	S	8
Meropenem	S	1
Amikacina	S	4

**Un numero, in assenza di valori di riferimento,
non ha significato in Medicina di Laboratorio**

Pseudomonas aeruginosa

S

I

R

Piperacillina	0,12	0,25	0,5	1	2	4	8	16	32	64	128	256
Ceftazidime	0,12	0,25	0,5	1	2	4	8	16	32	64	128	256
Cefepime	0,12	0,25	0,5	1	2	4	8	16	32	64	128	256
Imipenem	0,12	0,25	0,5	1	2	4	8	16	32	64	128	256
Meropenem	0,12	0,25	0,5	1	2	4	8	16	32	64	128	256
Aztreonam	0,12	0,25	0,5	1	2	4	8	16	32	64	128	256
Gentamicina	0,12	0,25	0,5	1	2	4	8	16	32	64	128	256
Amikacina	0,12	0,25	0,5	1	2	4	8	16	32	64	128	256
Tobramicina	0,12	0,25	0,5	1	2	4	8	16	32	64	128	256
Ciprofloxacina	0,12	0,25	0,5	1	2	4	8	16	32	64	128	256
Levofloxacina	0,12	0,25	0,5	1	2	4	8	16	32	64	128	256

Si facilita la scelta della migliore combinazione di antibiotici



2012

Bronco-alveolo lavaggio:

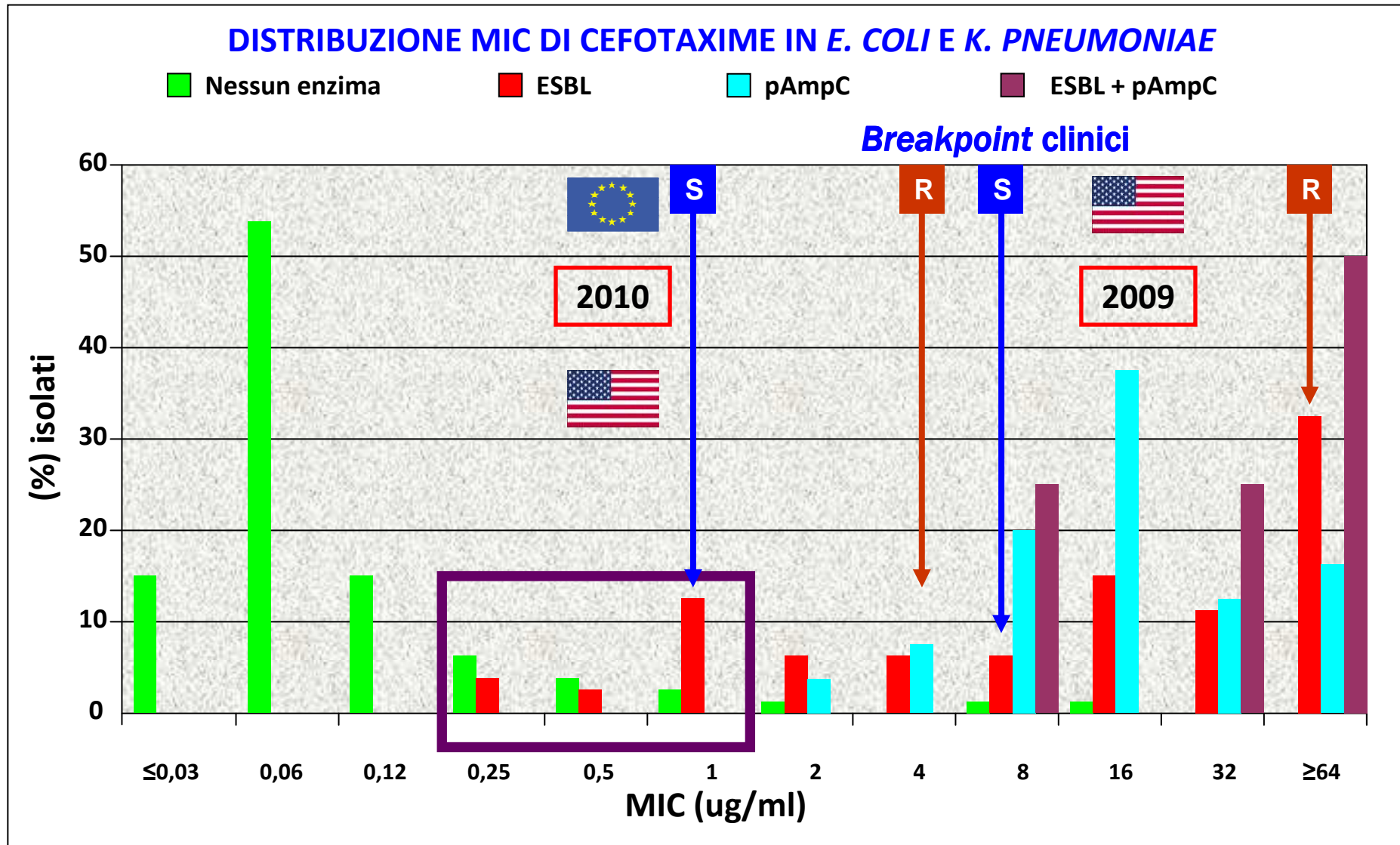
sviluppo di *E. coli*

Carica batterica: 10^6 UFC/ml

Farmaco	MIC (mg/L)	Categ.	Breakpoint	
			S	R
Ampicillina	≥ 32	R	≤ 8	> 8
Amoxi/Clav.	8/2	S	$\leq 8/2$	$> 8/2$
Piperacillina	4	S	≤ 8	> 16
Pipera/Tazob.	4/4	S	$\leq 8/4$	$> 16/4$
Cefotaxime	0,5	S	≤ 1	> 2
Ceftazidime	0,25	S	≤ 1	> 4
Imipenem	0,03	S	≤ 2	> 8
Gentamicina	1	S	≤ 2	> 4
Ciprofloxacina	0,5	S	$\leq 0,5$	> 1

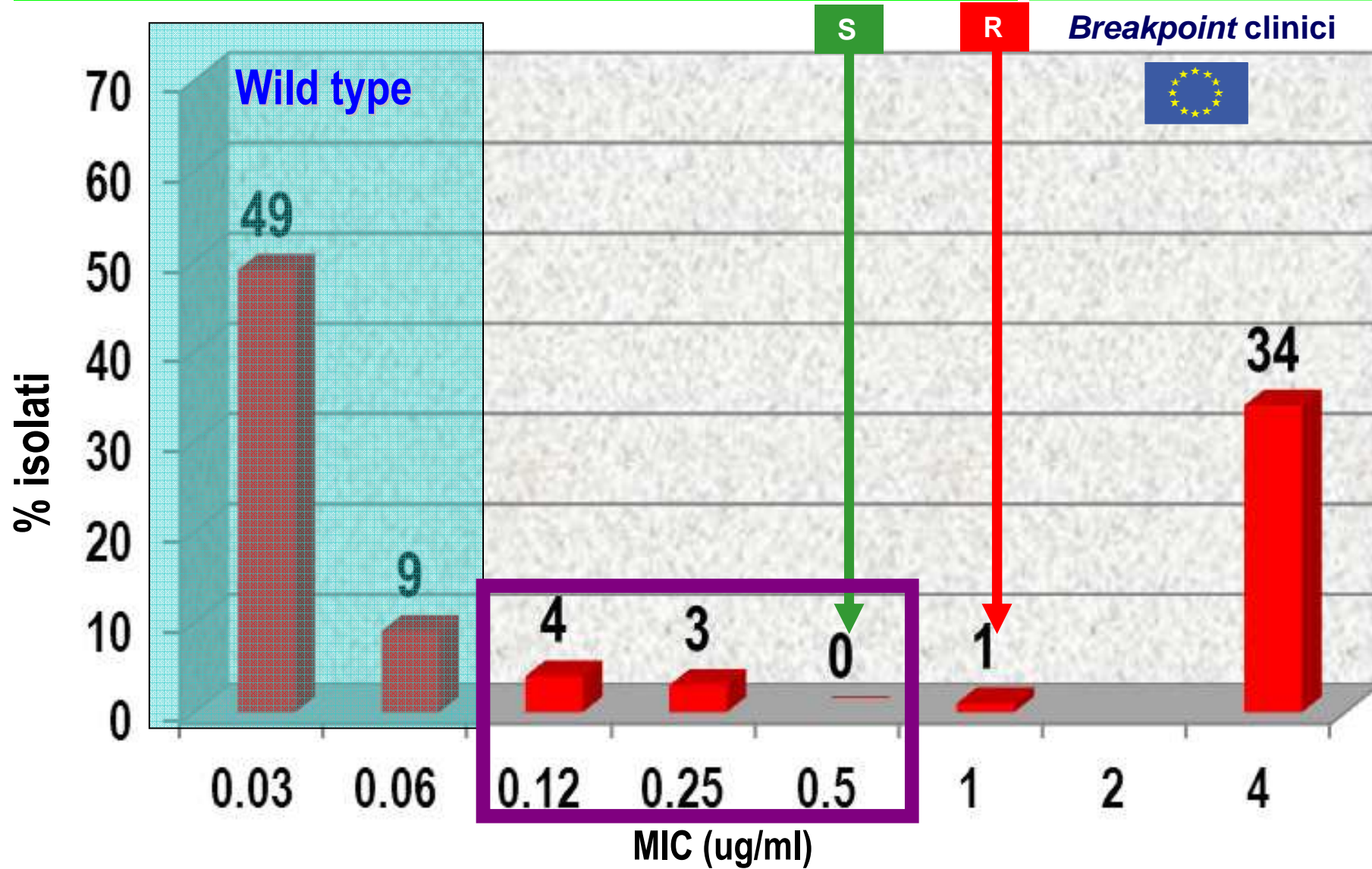
Cephalosporin MIC distribution of extended-spectrum- β -lactamase- and pAmpC-producing *Escherichia coli* and *Klebsiella* species.

Kohner PC, et al. J Clin Microbiol. 2009 Aug;47(8):2419-25.



CIPROFLOXACIN – ESCHERICHIA COLI UDINE 2013

612 isolati da
materiali nobili



EUCAST - Epidemiological cut-off: Wild type $\leq 0,064$ µg/ml

Predictors of Mortality in Patients with Bloodstream Infections Caused by Extended-Spectrum- β -Lactamase-Producing *Enterobacteriaceae*: Importance of Inadequate Initial Antimicrobial Treatment

Tumbarello M, et al. *Antimicrob Agents Chemother.* 2007 Jun;51(6):1987-94

TABLE 5. Mortality rates (21 day) in 9

The eight patients treated with a fluoroquinolone (ciprofloxacin in all cases) who died were infected by

Cs ranging from 0.5 to 1

mutation at codon 83 of detected in the other four.

Failure to reach the pharmacodynamic targets correlated with quinolone efficacy is more likely when the MIC of the drug used is close to the susceptibility breakpoint, particularly when low doses are administered.

For severely ill, hospitalized patients, a fixed dosage regimen of 400 mg twice daily (those prescribed for our patients) has been estimated to provide optimal pharmacodynamic exposure to ciprofloxacin only for organisms with ciprofloxacin MICs of < 0.03 g/ml.

For less susceptible pathogens (MICs of 0.25 to 0.5 g/ml), substantial dose increases or the addition of a second active agent must be considered.

1.48 (0.59-3.66)	0.40
0.55 (0.19-1.55)	0.24
0.14 (0.02-1.03)	0.01

Bronco-alveolo lavaggio

sviluppo di *E. coli*

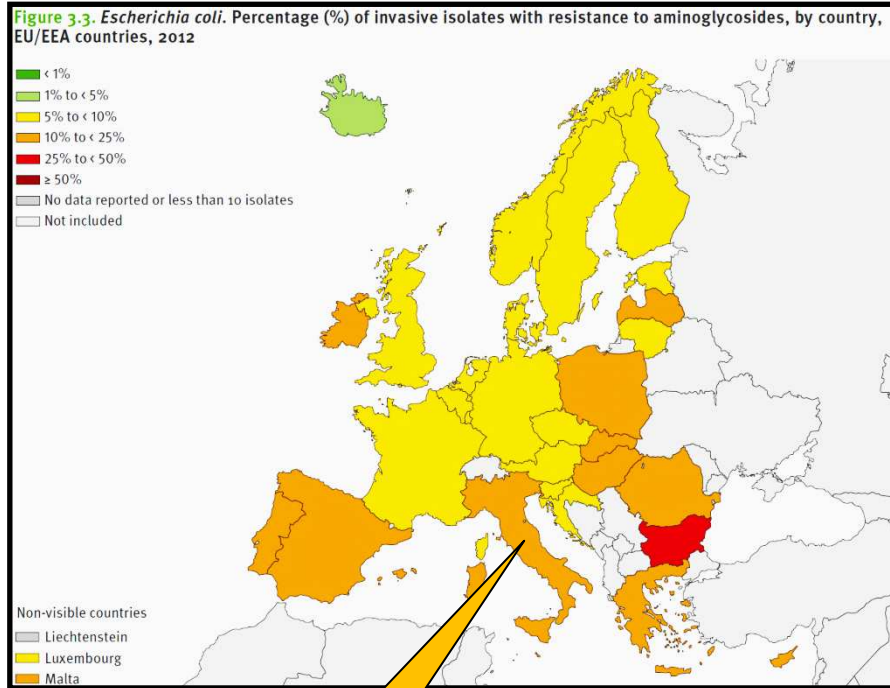
*** L'attività di questi antibiotici potrebbe richiedere l'utilizzo di dosaggi più elevati della norma o l'associazione con un secondo farmaco attivo.**

Utile una consulenza infettivologica

Farmaco	MI					
Ampicillina						
Amoxi/Clav.						
Piperacillina	4	S	0,5-8	≤8	> 16	
Pipera/Tazob.	4	S	0,5-8	≤8	>16	
Cefotaxime	0,5	S	0,016-0,25	*	≤1	>2
Ceftazidime	0,25	S	0.032-0,5	≤1	>4	
Imipenem	0,03	S	0,032-0,5	≤2	>8	
Gentamicina	1	S	0,125-2	≤2	>4	
Ciprofloxacina	0,5	S	0,004-0,06	*	≤0,5	>1

EARS-NET 2012: (%) of invasive isolates with resistance to Aminoglycosides

Escherichia coli



21.4%

UDINE

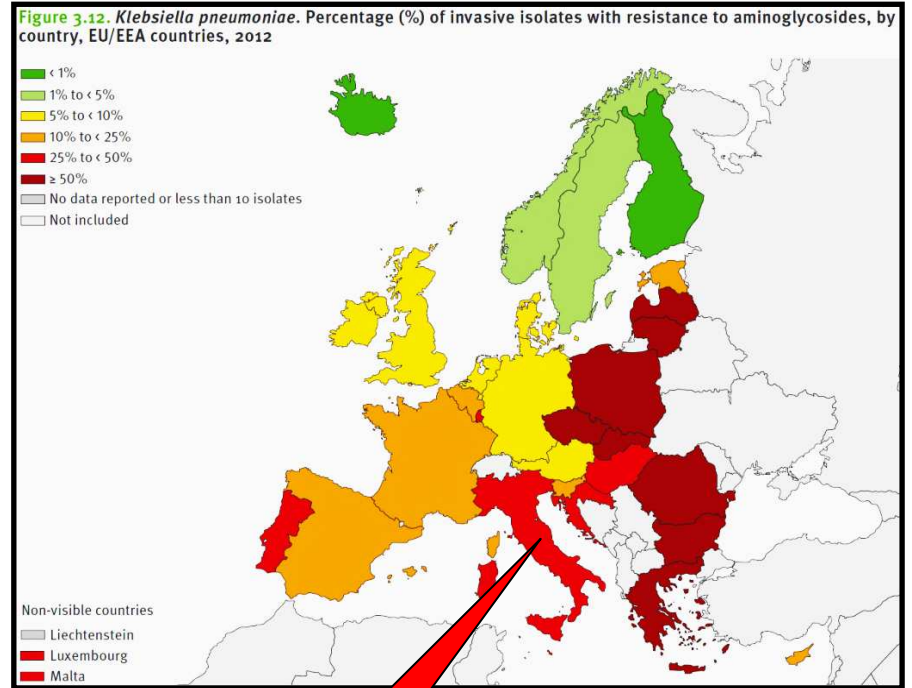
5%

TREVISO

3%

2013

Klebsiella pneumoniae



42.2%

UDINE

7%

TREVISO

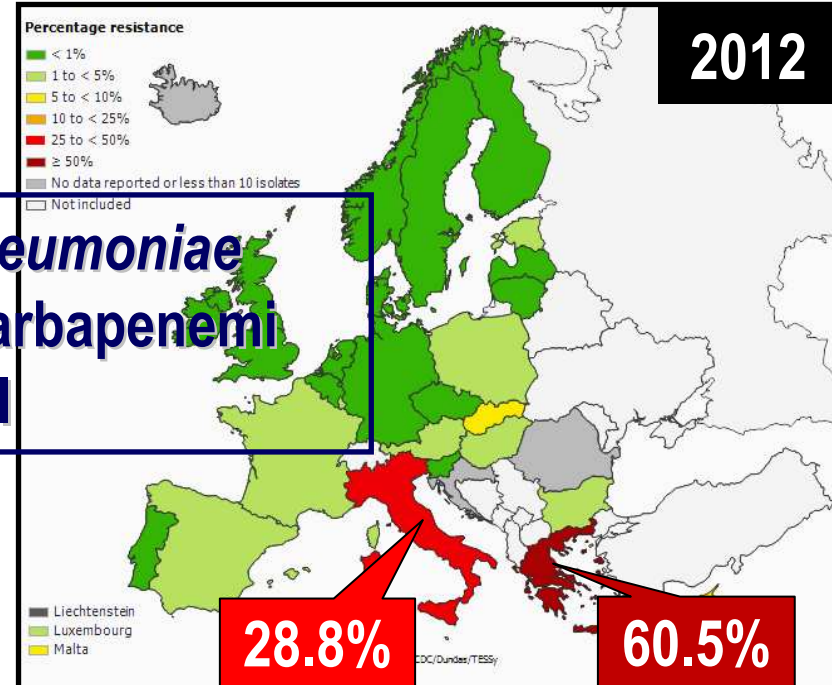
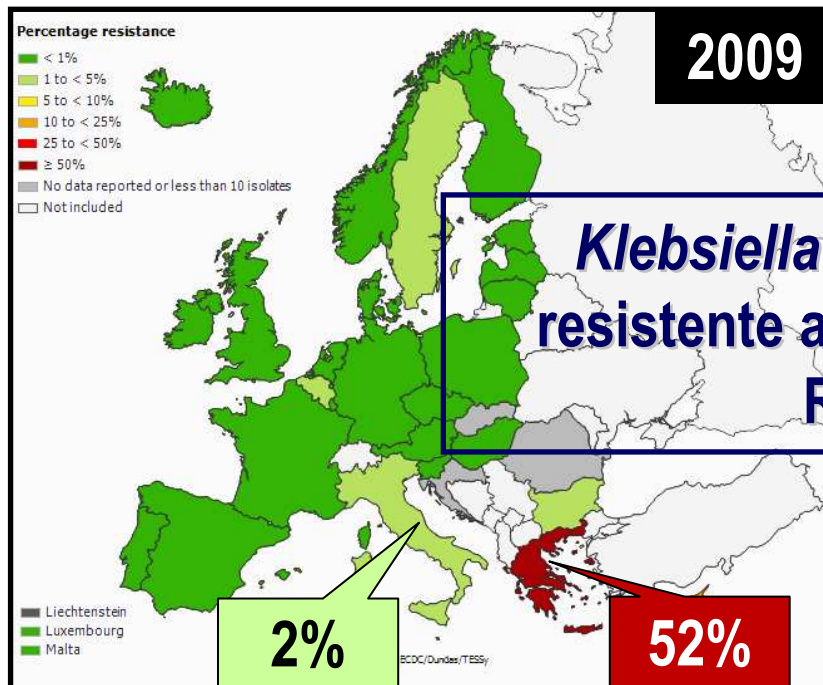
6%

ENTEROBATTERI: Meccanismi di resistenza ai carbapenemi

ESBL o
produzione di AmpC
+
perdita di porine

Produzione di
metallo- β -lattamasi
(VIM, IMP, NDM)

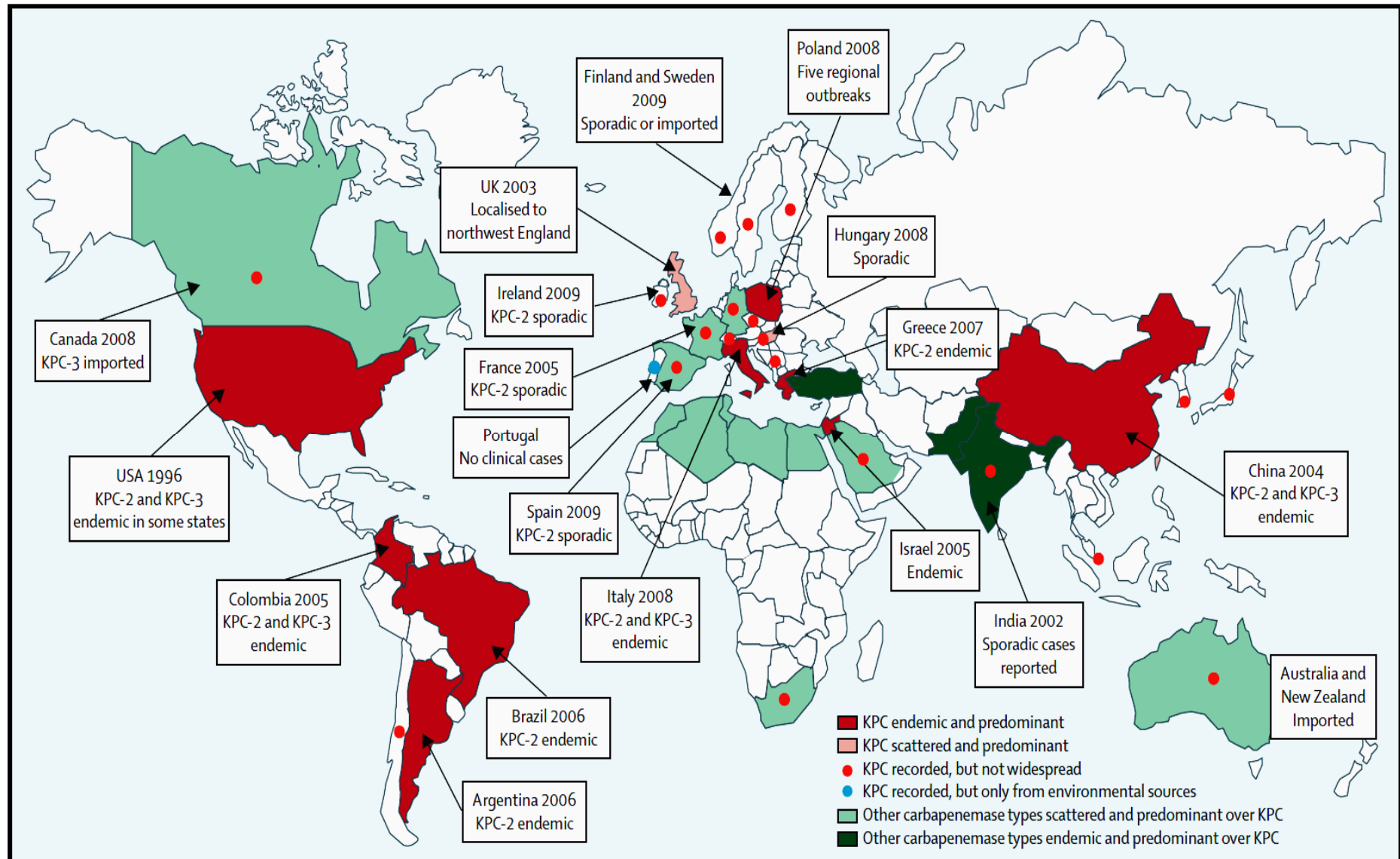
Produzione di
carbapenemasi
a serina
(KPC, SME, IMI, OXA)



Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases

Munoz-Price LS., et al. Lancet Infect Dis 2013 Sep;13(9):785-96

Figure: Epidemiological features of producers of *Klebsiella pneumoniae* carbapenemases by country of origin



The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria

Lancet Infect Dis 2009;
9: 228–36

Patrice Nordmann, Gaëlle Cuzon, Thierry Naas

Negli enterobatteri KPC-positivi,
la MIC per i carbapenemi varia
da 0.25 mg/L a valori superiori a 32 mg/L

	<i>K pneumoniae</i> ^{8,17} 43,45,54,55,62	<i>E coli</i> ^{23,27,44,51}	*Other enterobacterial isolates ^{9,10,26,36,37,51}	<i>Paeruginosa</i> ^{47,62}
Imipenem†	2 to >32	1 to 32	4 to >32	>32
Imipenem+CLA	0.5 to >32	0.25 to 2	2 to 4	2 to >32
Meropenem†	1 to >32	0.25 to >32	2 to 32	>32
Meropenem+CLA	1 to >32	0.094 to 0.38	4	3 to >32
Ertapenem†	8 to >32	1 to >32	4 to 16	>32
Ertapenem+CLA	2 to >32	0.25 to 4	..	2 to >32

Enterobatteri e carbapenemi



Marzo 2012

Indicazioni per la conferma fenotipica della produzione di carbapenemasi nelle Enterobacteriaceae

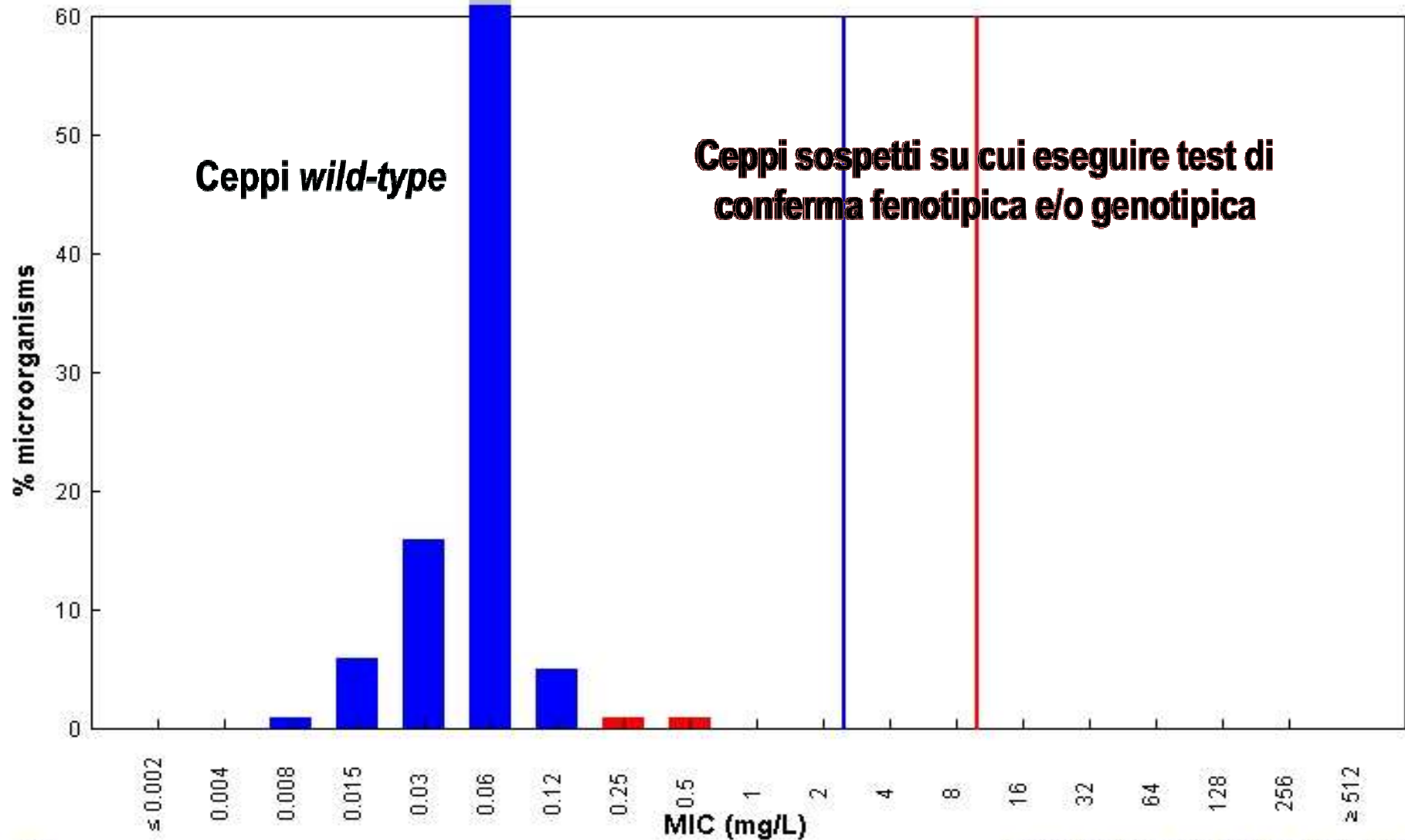
Nella comune pratica di laboratorio è consigliabile sospettare la produzione di carbapenemasi in presenza di una ridotta sensibilità al meropenem:

Meropenem MIC \geq 0.5 mg/L

(diametro dell'alone di inibizione \leq 25 mm)

Meropenem / *Klebsiella pneumoniae*
EUCAST MIC Distribution - Reference Database 2013-05-28

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 ≤ 0.125 mg/L

18171 observations (67 data sources)
Clinical breakpoints: S ≤ 2 mg/L, R > 8 mg/L

CONFERMA FENOTIPICA DELLA PRODUZIONE DI CARBAPENEMASI NEGLI ENTEROBATTERI

**Meropenem
MIC $\geq 0,5$ ug/ml**

**Test di Hodge
modificato**

Ac. fenilboronico

**1. EDTA
2. Ac. dipicolinico**

DISTORSIONE

**Carbapenemasi
non specificata**

DIAMETRO ≥ 5 mm

KPC
Possibile falsa positività
dovuta alla presenza di
AmpC

DIAMETRO ≥ 5 mm

**Metallo
beta-lattamasi**

Test di Hodge modificato



Test di Hodge = positivo

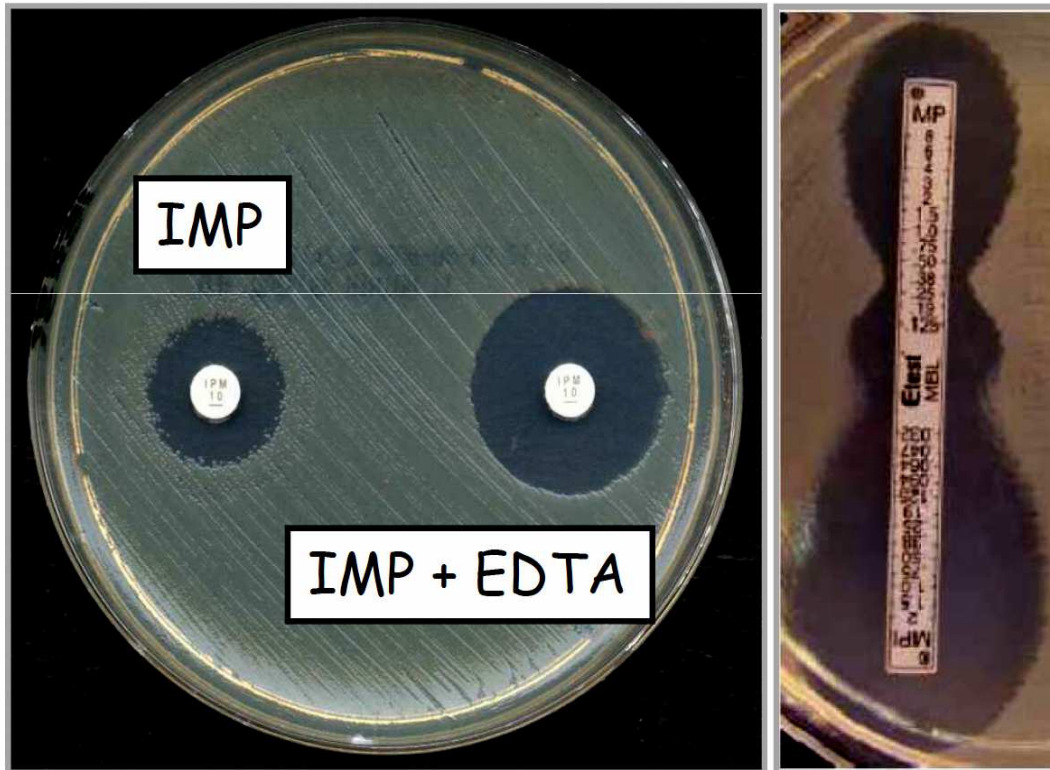
Allestire una sospensione 0,5 McFarland in soluzione fisiologica con *E. coli* ATCC25922 e seminare a tutta piastra su Mueller-Hinton agar.

Dopo 15' posizionare al centro della piastra un dischetto di meropenem (nel caso di ceppi con MIC imipenem > MIC meropenem può essere opportuna l'esecuzione del test utilizzando anche un dischetto di imipenem), con l'ansa raccogliere il ceppo da testare (da 1 a 2 colonie), deporle in prossimità del dischetto di antibiotico e strisciare (o inoculare tagliando con l'ansa la superficie dell'agar) in linea retta allontanandosi dal dischetto verso il bordo della piastra. Incubare a $35 \pm 2^\circ\text{C}$ per 18 ore.

Test fenotipici per la conferma di MBL

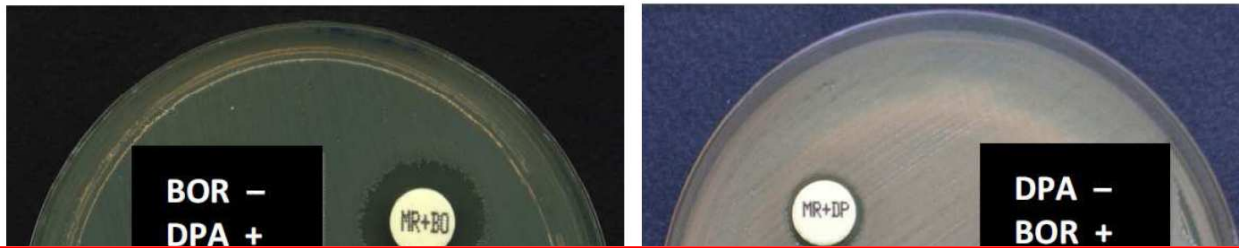
Test di sinergia con EDTA positivo

Dischi di combinazione Etest



Etest positivo se:
riduzione della MIC di
meropenem + EDTA
 ≥ 3 diluizioni al raddoppio
rispetto al solo meropenem
o presenza di
"zona fantasma"

Carbapenemasi: test fenotipici di conferma



“Ceppo produttore di carbapenemasi; la terapia con carbapenemi potrebbe risultare scarsamente efficace o inefficace anche se “in vitro” il ceppo appare sensibile a questi farmaci.

Nel caso in cui si intendano utilizzare tali farmaci si raccomanda una preventiva consulenza con un esperto di terapia antibiotica”.



- MBL: BOR -, DPA +
- KPC: DPA -, BOR +
- OXA-48: DPA -, BOR - CLO -

Klebsiella pneumoniae (da materiali nobili)

DISTRIBUZIONE MIC 2013

2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
TV	AMOXI/CLAV	237	67						17	38	5	7	33				
UD	AMOXI/CLAV	150	93						69	10	13	1	7				
TV	PIPERAZAZO	237	78						4	39	24	11	8	1	1	2	10
UD	PIPERAZAZO	150	78						6	49	15	8	3	3	3	0	13
TV	CEFOTAXIME	237	73		64	4	2	2	1	1	1	5	1	3	16		
UD	CEFOTAXIME	150	85		72	6	4	3	0	0	0	5	1	1	8		
TV	CEFTAZIDIME	237	70			38	26	5	1	3	3	3	4	7	3	2	5
UD	CEFTAZIDIME	150	80			50	22	7	1	1	3	3	1		3	7	2
TV	CIPROFLOXACINA	237	70	53	9	4	2	2	2	1	27						
UD	CIPROFLOXACINA	150	82	64	12	2	1	3	2	1	15						
TV	LEVOFLOXACINA	237	71			53	3	3	12	0	2	27					
UD	LEVOFLOXACINA	150	84			66	2	5	11	1	3	12					
2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256

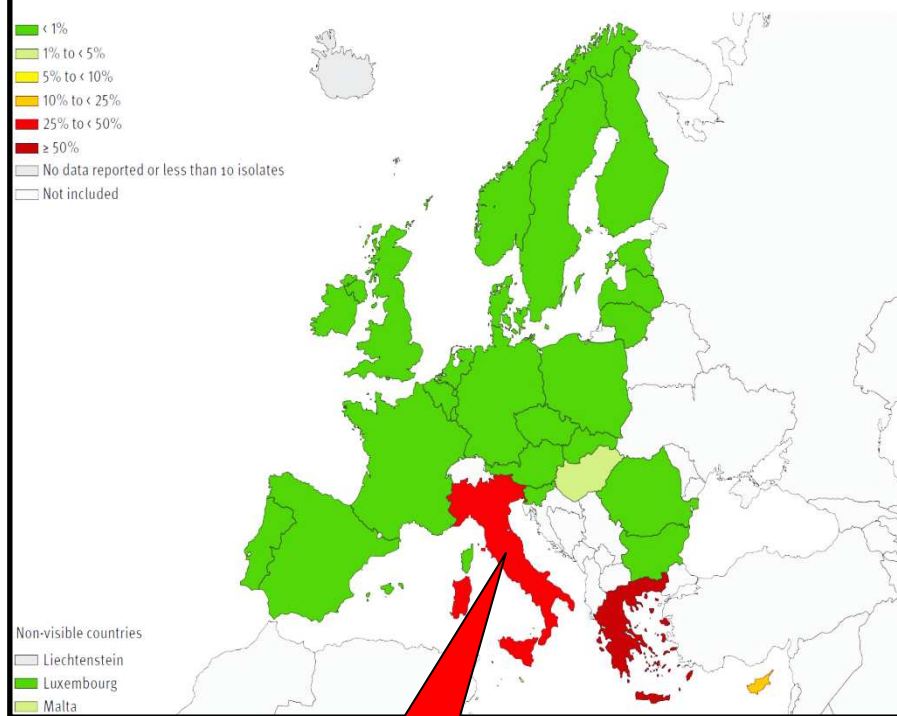
Klebsiella pneumoniae (da materiali nobili)

DISTRIBUZIONE MIC 2013

2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
TV	AMIKACINA	237	94						57	13	21	3	3	3			
UD	AMIKACINA	150	93						69	10	13	1	3	4			
TV	TRIMET/SULFA	237	76		23	30	5	13	3	2	0	24					
UD	TRIMET/SULFA	150	80		31	26	5	14	3	1	1	19					
TV	NITROFURANTOINA	237	94								1	11	22	45	15	6	
UD	NITROFURANTOINA	150	89								2	9	25	44	9	11	
TV	TIGECICLINA	237	98			15	63	13	7	2							
UD	TIGECICLINA	150	96			19	59	13	5	4							
TV	ERTAPENEM	237	96		86	5	3	2	0	0	4						
UD	ERTAPENEM	150	92		84	4	3	1	0	1	7						
TV	MEROPENEM	237	96			95	1	0	0	0	0	0	0	0	4		
UD	MEROPENEM	150	93			91	1	0	0	1	0	0	1	1	5		
TV	COLISTINA	237	98				37	56	4	0	0	2					
UD	COLISTINA	150	96				69	26	1	0	0	4					
2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256

EARS-NET: *Klebsiella pneumoniae*: percentage (%) of invasive isolates with resistance to carbapenems

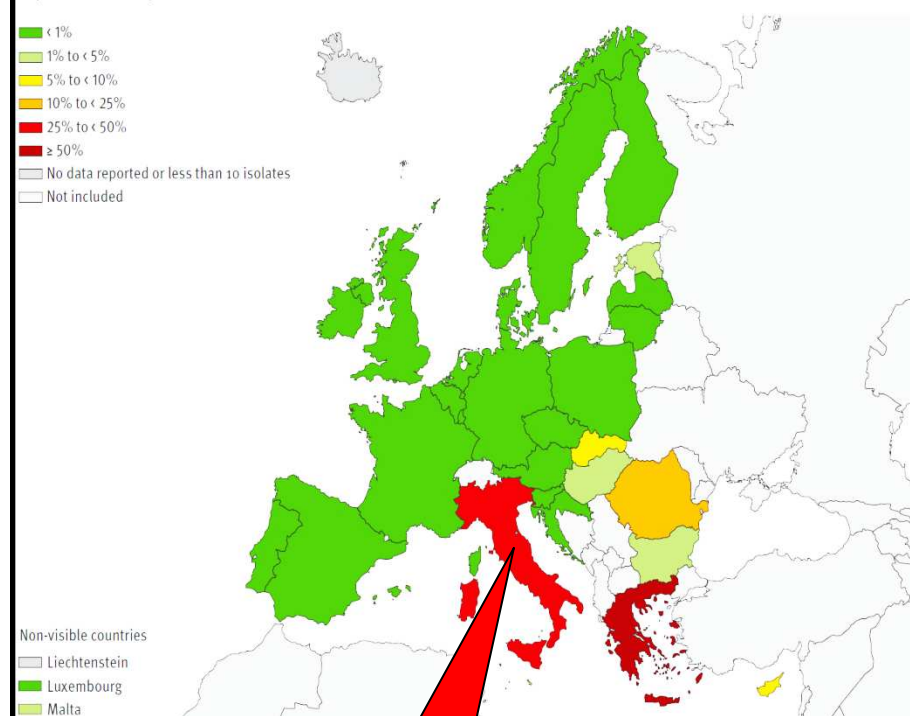
Figure 4.12: *Klebsiella pneumoniae*: percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2011



26.7%

2011

Figure 3.13: *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2012



28.8%

2012

Klebsiella pneumoniae (da materiali nobili)

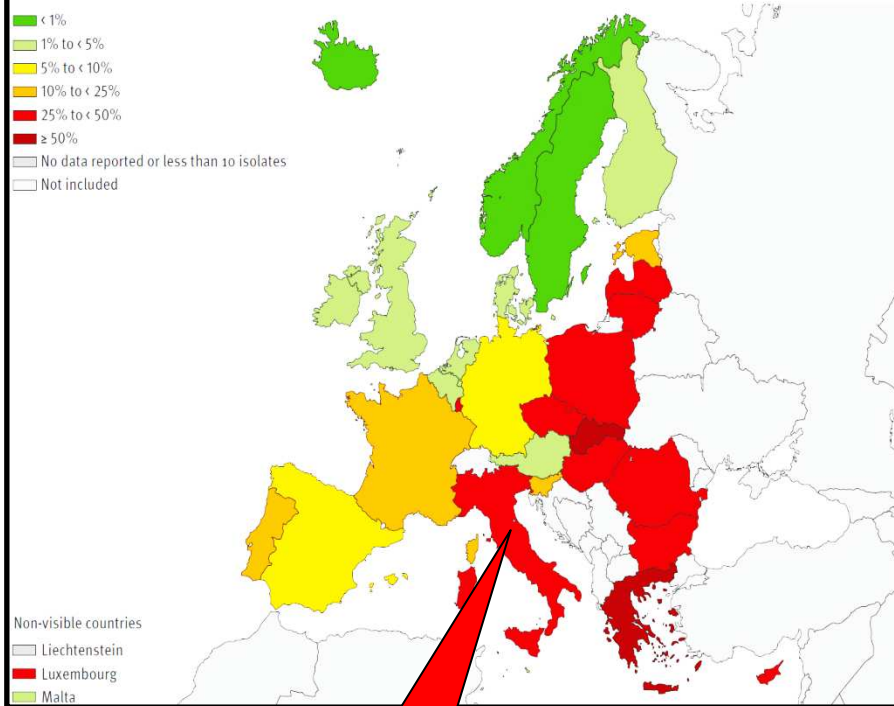
DISTRIBUZIONE MIC

2013

2013	Antimicrobico	N. Ceppi	% S	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64
CO	MEROPENEM	70	100		98	2								
CO	COLISTINA	70	100			30	67	3						
RO	MEROPENEM	102	86		84	0	0	0	2	0	0	2	12	
RO	COLISTINA	102	91			45	36	9	1	0	9			
VI	MEROPENEM	267	81		79	0	0	1	1	1	1	1	5	11
VI	COLISTINA	267	94			52	39	2	1	0	6			
ME	MEROPENEM	459	48		42	1	1	1	3	12	6	6	18	10
ME	COLISTINA	459	76			34	37	4	1	0	24			
2013	Antimicrobico	N. Ceppi	% S	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64

EARS-NET: *Klebsiella pneumoniae*: percentage (%) of invasive isolates with combined resistance (resistance to third generation cephalosporins, fluoroquinolones and aminoglycosides)

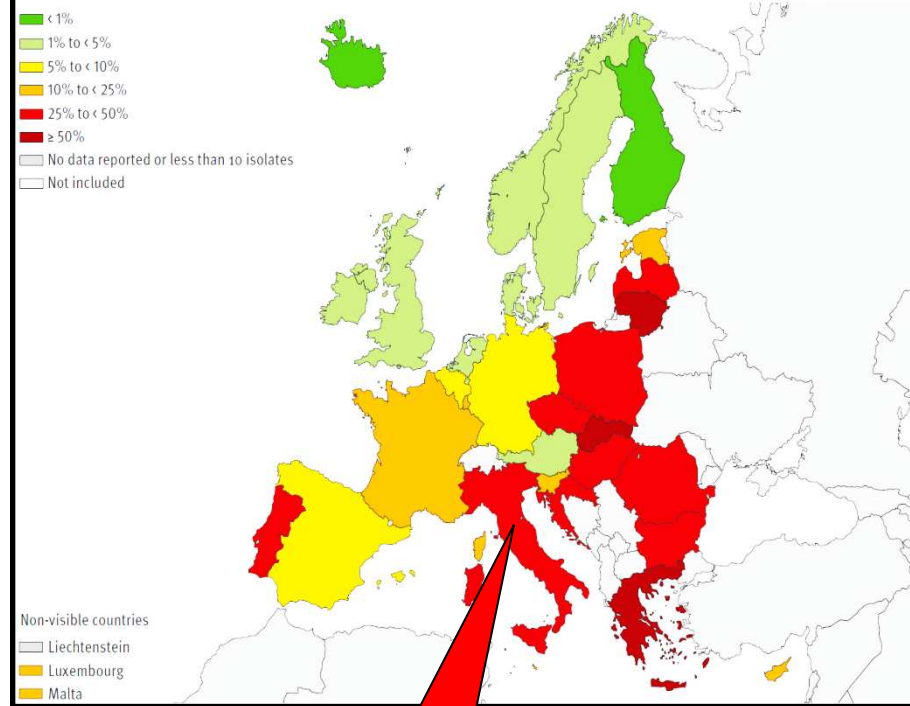
Figure 4.13: *Klebsiella pneumoniae*: percentage (%) of invasive isolates with combined resistance (resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides), by country, EU/EEA countries, 2011



32.9%

2011

Figure 3.14: *Klebsiella pneumoniae*. Percentage (%) of invasive isolates with combined resistance (resistance to third-generation cephalosporins, fluoroquinolones and aminoglycosides), by country, EU/EEA countries, 2012



40.0%

2012

Klebsiella pneumoniae

Epidemiologia 2012
UDINE

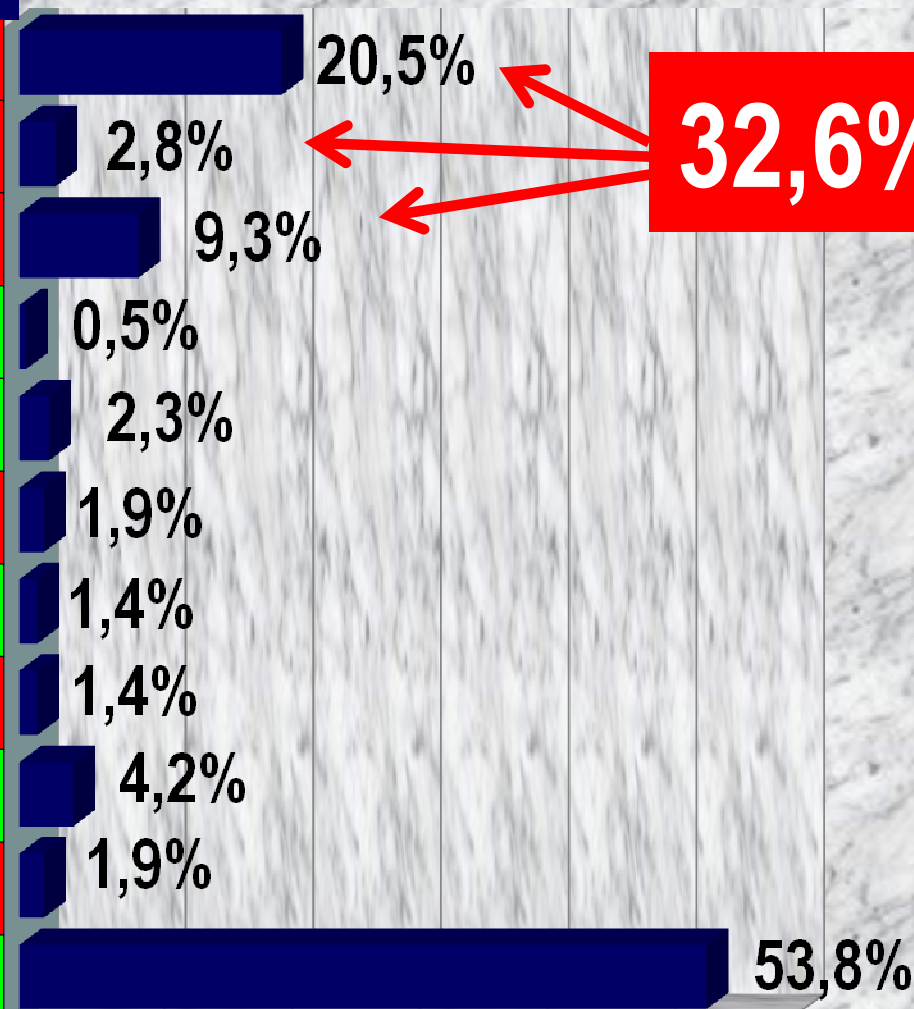
127 isolati da
materiali nobili

Breakpoint
Clinici 2012



FENOTIPO AST

AK: R	CAZ: R	CIP: R	ME: R	P/T: R
AK: R	CAZ: R	CIP: R	ME: S	P/T: R
AK: S	CAZ: R	CIP: R	ME: S	P/T: R
AK: R	CAZ: R	CIP: S	ME: S	P/T: S
AK: S	CAZ: R	CIP: R	ME: S	P/T: S
AK: S	CAZ: R	CIP: S	ME: S	P/T: R
AK: S	CAZ: R	CIP: S	ME: S	P/T: S
AK: S	CAZ: S	CIP: R	ME: S	P/T: R
AK: S	CAZ: S	CIP: R	ME: S	P/T: S
AK: S	CAZ: S	CIP: S	ME: S	P/T: R
AK: S	CAZ: S	CIP: S	ME: S	P/T: S



Klebsiella pneumoniae

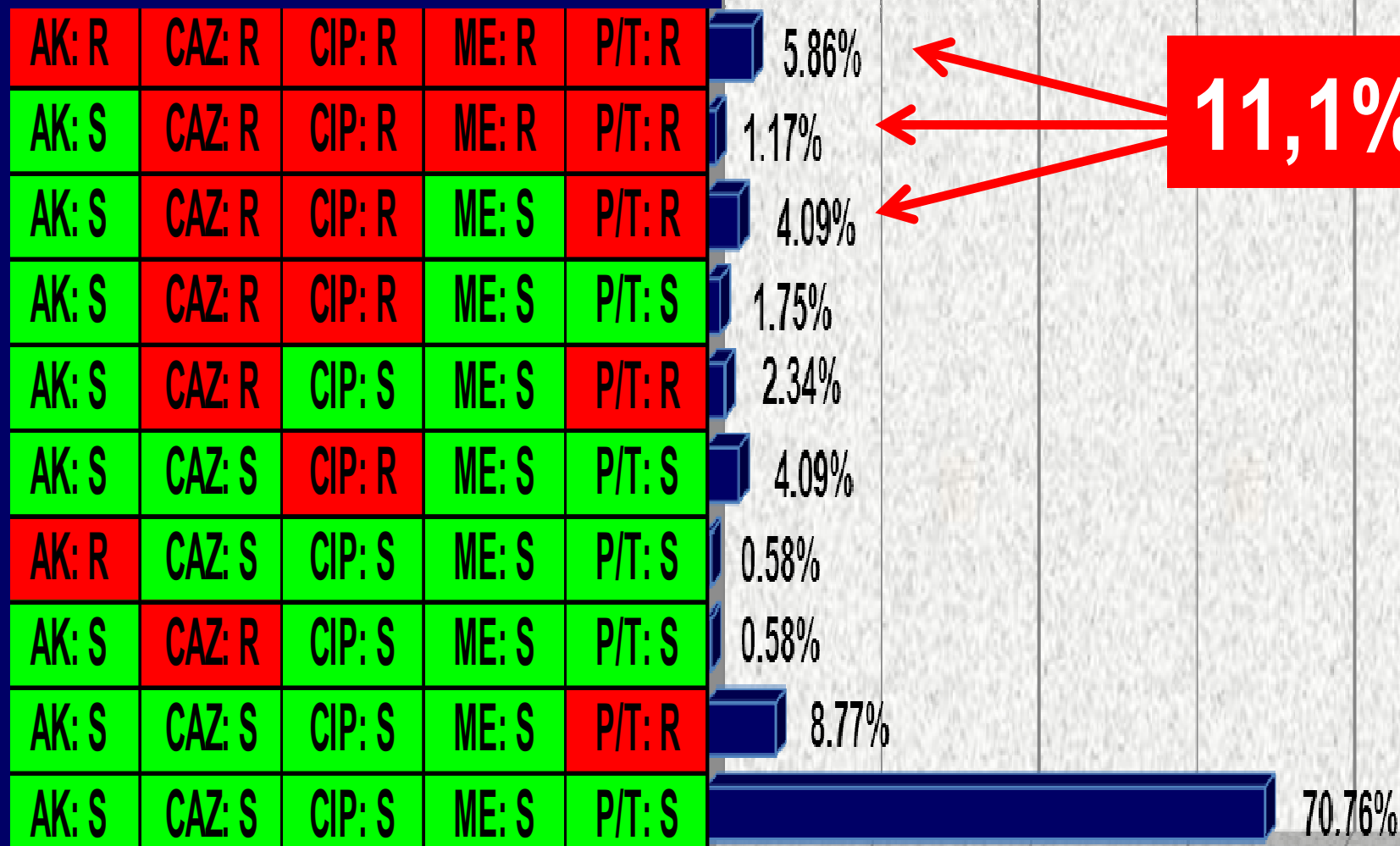
Epidemiologia 2013
UDINE

150 isolati da
materiali nobili

Breakpoint
Clinici 2013



FENOTIPO AST



Proteus mirabilis (da materiali nobili)

DISTRIBUZIONE MIC 2013

2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
TV	AMOXI/CLAV	162	61						15	31	8	7	39				
UD	AMOXI/CLAV	27	78						33	30	7	8	22				
TV	PIPERA/TAZO	162	95						55	26	12	2	0	0	0	1	4
UD	PIPERA/TAZO	27	100						78	15	7						
TV	CEFOTAXIME	162	58		52	3	0	1	2	4	2	8	1	2	25		
UD	CEFOTAXIME	27	92		85	3	0	4	0	0	0	4	0	0	4		
TV	CEFTAZIDIME	162	64			54	3	5	2	4	2	4	25	1			
UD	CEFTAZIDIME	27	93			74	19	0	0	0	0	0	7				
TV	CIPROFLOXACINA	162	37	24	9	1	2	1	1	12	50						
UD	CIPROFLOXACINA	27	52	33	11	0	4	4	7	15	26						
TV	LEVOFLOXACINA	162	37			27	1	2	7	1	0	62					
UD	LEVOFLOXACINA	27	66			37	0	7	22	8	0	26					
2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256

Proteus mirabilis (da materiali nobili)

DISTRIBUZIONE MIC 2013

2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
TV	AMIKACINA	162	94						2	18	57	17	4	2			
UD	AMIKACINA	27	100						4	29	41	26					
TV	TRIMET/SULFA	162	33		2	15	5	6	3	2	4	63					
UD	TRIMET/SULFA	27	29		7	15	0	7	0	0	4	67					
TV	NITROFURANTOINA	162	35											7	28	65	
UD	NITROFURANTOINA	27	37											37	63		
TV	ERTAPENEM	162	100		97	2	1										
UD	ERTAPENEM	27	100		98	2											
TV	MEROPENEM	162	100			89	5	2	2	2							
UD	MEROPENEM	27	100			93	7										
2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256

Enterobacter cloacae (da materiali nobili)

DISTRIBUZIONE MIC 2013

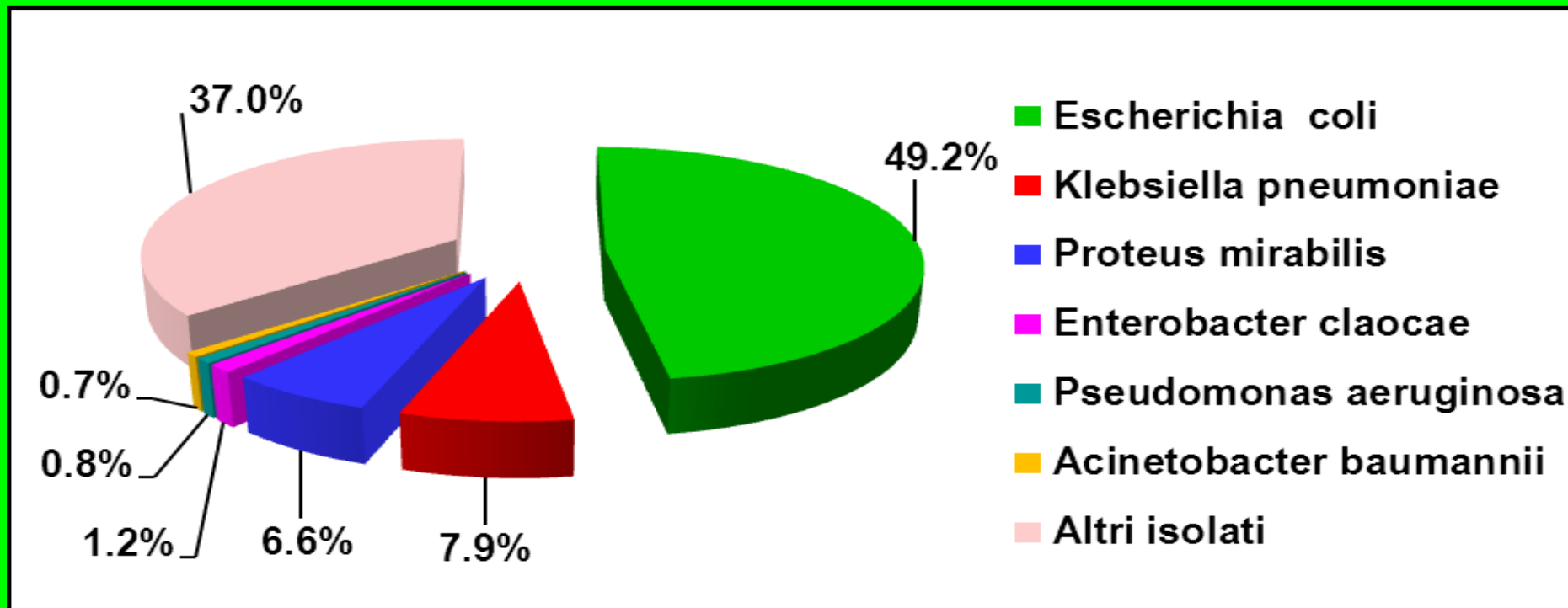
2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
TV	PIPERA/TAZO	133	90						17	58	9	6	2	2	0	4	2
UD	PIPERA/TAZO	88	80						25	48	5	2	0	6	9	3	2
TV	CEFOTAXIME	133	83		8	31	36	6	2	0	2	3	1	2	9		
UD	CEFOTAXIME	88	77		14	34	19	8	2	1	3	1	0	4	14		
TV	CEFTAZIDIME	133	86			14	56	12	4	1	1	1	2	2	5	2	
UD	CEFTAZIDIME	88	78			26	41	10	1	0	0	1	2	7	6	4	2
TV	CIPROFLOXACINA	133	94	80	10	1	0	3	0	2	4						
UD	CIPROFLOXACINA	88	93	74	16	2	1	0	0	0	7						
TV	LEVOFLOXACINA	133	93			80	1	2	10	0	2	5					
UD	LEVOFLOXACINA	88	93			78	8	5	2	3	0	4					
2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256

Enterobacter cloacae (da materiali nobili)

DISTRIBUZIONE MIC 2013

2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
TV	AMIKACINA	133	100						77	11	12						
UD	AMIKACINA	88	100						86	8	5	1					
TV	TRIMET/SULFA	133	91		46	32	3	9	0	1	0	9					
UD	TRIMET/SULFA	88	98		42	32	2	16	5	1	0	2					
TV	NITROFURANTOINA	133	95									4	6	48	37	5	
UD	NITROFURANTOINA	88	99								1	3	20	55	20	1	
TV	TIGECICLINA	133	97			15	73	8	1	1	2						
UD	TIGECICLINA	88	99			26	62	6	5	1							
TV	ERTAPENEM	133	96		79	7	4	6	2	2							
UD	ERTAPENEM	88	95		74	4	6	11	4	1							
TV	MEROPENEM	133	100			98	0	1	1								
UD	MEROPENEM	88	100			98	2										
TV	COLISTINA	133	92				67	20	4	1	2	6					
UD	COLISTINA	88	95				70	23	1	1	1	4					
2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256

UDINE 2013 - Batteri Gram negativi (da urine)



Microrganismo	N° Isolati	ESBL	AMPc	CBPEN	COL: R
Escherichia coli	49.2%	11.1%	0.3%	/	/
Klebsiella pneumoniae	7.9%	10.9%	4.2%	3.9%	/
Proteus mirabilis	6.6%	4.7%	1.0%	/	/
Enterobacter cloacae	1.2%	4.2%	22.5%	1.4%	/
Pseudomonas aeruginosa	0.8%			60.9%	/
Acinetobacter baumannii	0.7%			50.0%	5,3% R

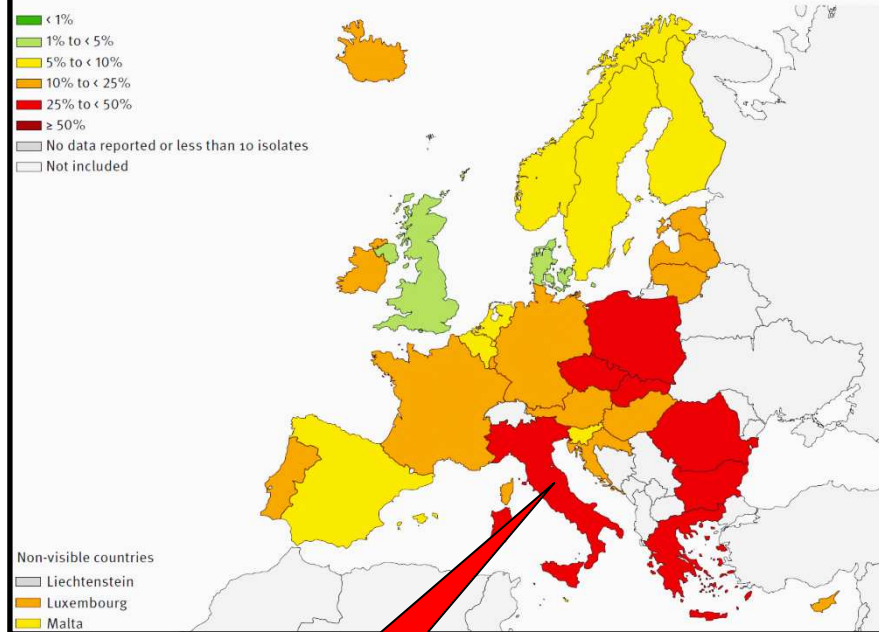
EARS-NET 2012: *Pseudomonas aeruginosa*

% of invasive isolates with resistance to:

Piperacillin ± tazobactam

Ceftazidime

Figure 3-20. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with resistance to piperacillin (±tazobactam), by country, EU/EEA countries, 2012



30%

UDINE

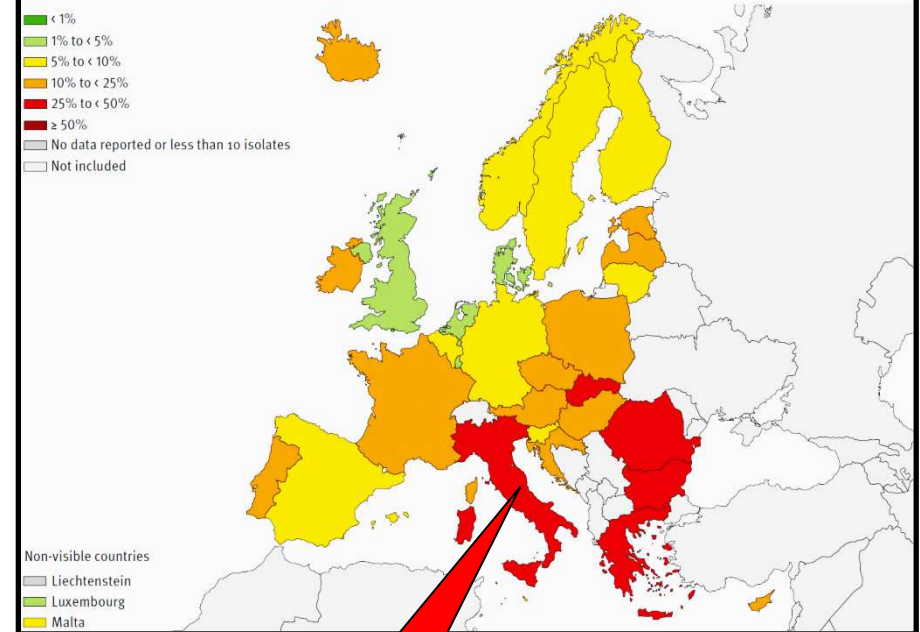
34%

TREVISO

39%

2013

Figure 3-21. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with resistance to ceftazidime, by country, EU/EEA countries, 2012



25.5%

UDINE

28%

TREVISO

32%

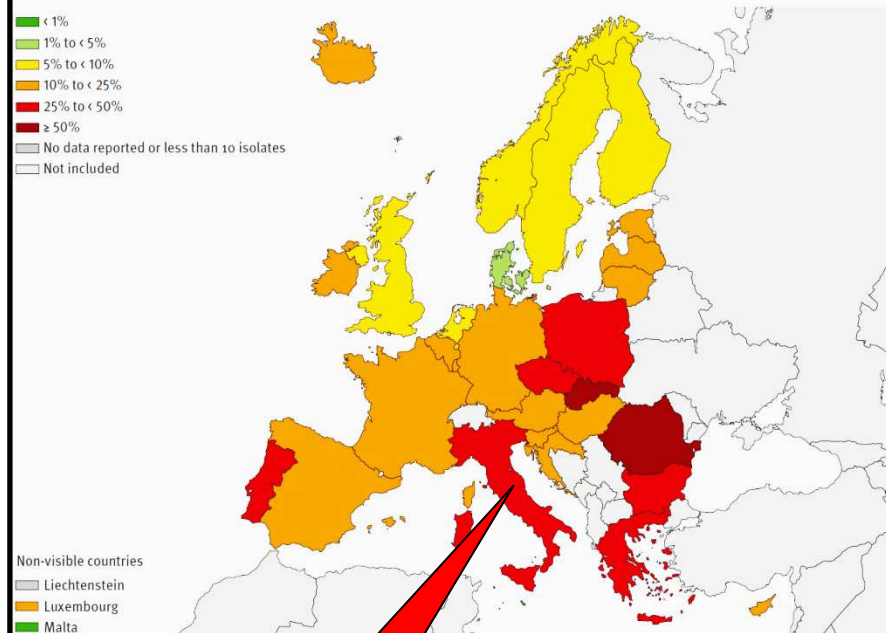
EARS-NET 2012: *Pseudomonas aeruginosa*

% of invasive isolates with resistance to:

Fluoroquinolones

Aminoglycosides

Figure 3.22. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with resistance to fluoroquinolones, by country, EU/EEA countries, 2012



31%

UDINE

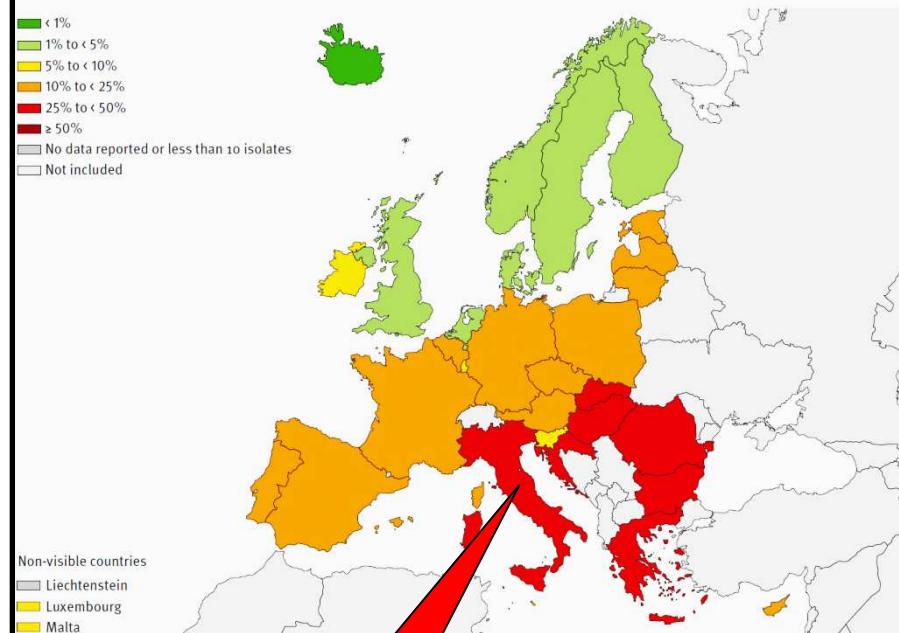
51%

TREVISO

49%

2013

Figure 3.23. *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with resistance to aminoglycosides, by country, EU/EEA countries, 2012



30%

UDINE

17%

TREVISO

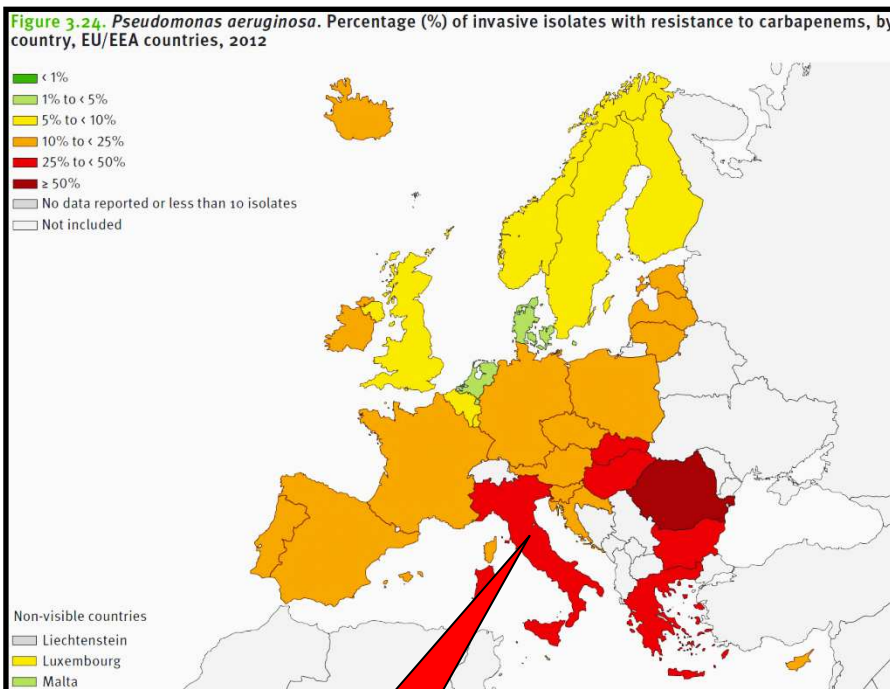
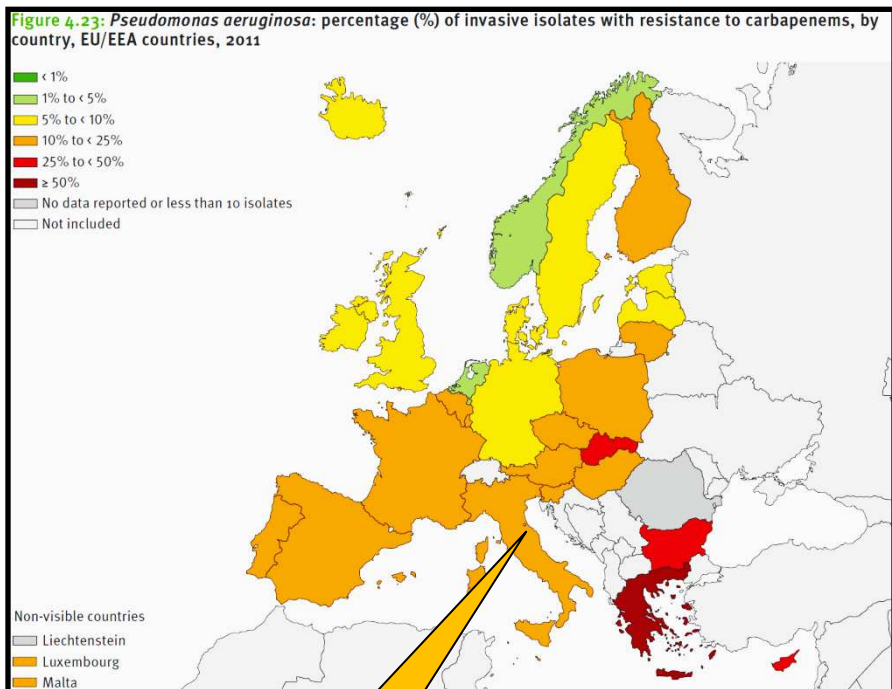
5%

EARS-NET 2012: *Pseudomonas aeruginosa*

% of invasive isolates with resistance to Carbapenems:

2011

2012



21%

25%

UDINE

33%

2012

TREVISO

28.5%

UDINE

39%

2013

TREVISO

33%

Pseudomonas aeruginosa (da materiali nobili)

DISTRIBUZIONE MIC 2013

2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256
TV	PIPERATAZO	765	61						3	13	25	10	10	8	6	12	13
UD	PIPERATAZO	460	66						3	18	27	8	10	5	5	10	14
TV	CEFTAZIDIME	765	68			1	2	5	26	16	13	5	9	10	8	4	1
UD	CEFTAZIDIME	460	72			1	1	8	33	14	9	6	6	7	8	6	1
TV	CIPROFLOXACINA	765	52	2	8	25	9	8	8	6	34						
UD	CIPROFLOXACINA	460	50	1	13	25	5	6	8	6	36						
TV	LEVOFLOXACINA	765	51			4	19	13	15	8	6	35					
UD	LEVOFLOXACINA	460	49			4	25	7	13	7	9	35					
TV	AMIKACINA	765	95						22	34	31	8	2	3			
UD	AMIKACINA	460	83						20	31	23	9	5	12			
TV	MEROPENEM	765	67			15	15	14	14	9	5	14	9	3	2		
UD	MEROPENEM	460	61			16	16	15	10	4	6	7	16	4	6		
TV	COLISTINA	765	99				2	5	55	36	1	1					
UD	COLISTINA	460	99				2	4	50	41	2	1					
2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64	128	256

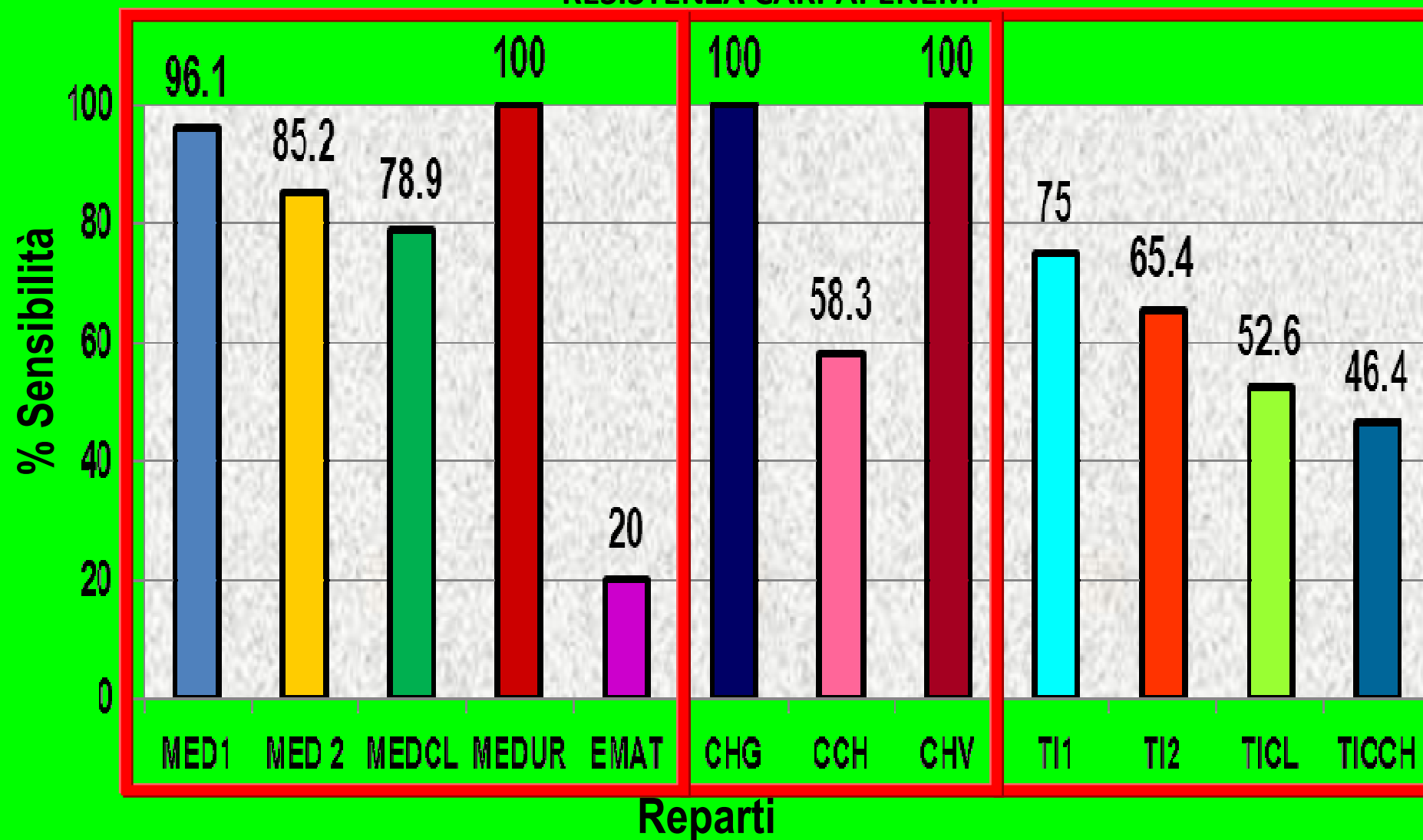
Pseudomonas aeruginosa (da materiali nobili)

DISTRIBUZIONE MIC 2013

2013	Antimicrobico	N. Ceppi	% S	0.12	0.25	0.5	1	2	4	8	16	32	64	128
PO	MEROPENEM	314	80	20	24	15	17	4	5	4	6	4	1	
PO	COLISTINA	314	98		2	4	37	50	5	2				
CO	MEROPENEM	438	78	16	28	15	12	7	5	9	5	2	1	
CO	COLISTINA	438	100		2	9	40	46	3					
VI	MEROPENEM	853	73	12	14	23	16	8	7	7	7	3	3	
VI	COLISTINA	853	98		2	4	53	35	4	2				
ME	MEROPENEM	1313	73	18	19	19	11	6	6	10	5	2	4	
ME	COLISTINA	1313	92		2	6	47	34	3	8				
RO	MEROPENEM	374	58	11	17	14	10	6	8	12	14	4	4	
RO	COLISTINA	374	98		2	2	40	50	4	2				
2013	Antimicrobico	N. Ceppi	% S	0.12	0.25	0.5	1	2	4	8	16	32	64	128

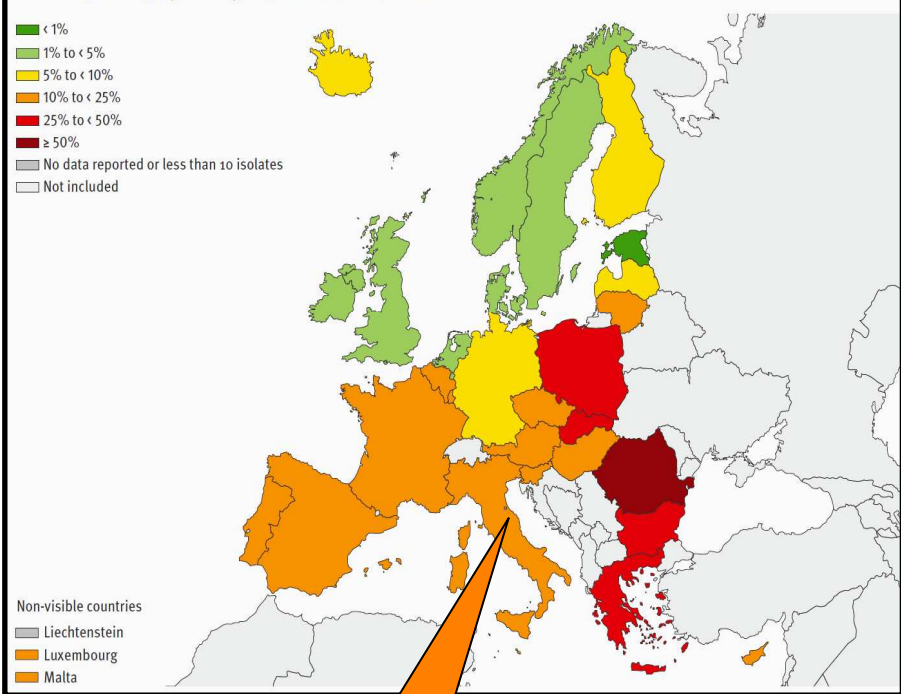
Pseudomonas aeruginosa

DISTRIBUZIONE PER REPARTO
RESISTENZA CARPAPENEMI



EARS-NET 2012: *Pseudomonas aeruginosa*: (%) of invasive isolates with combined resistance (resistance to three or more antimicrobial classes among Piperacillin (\pm Tazobactam), Ceftazidime, Fluoroquinolones, Aminoglycosides and Carbapenems)

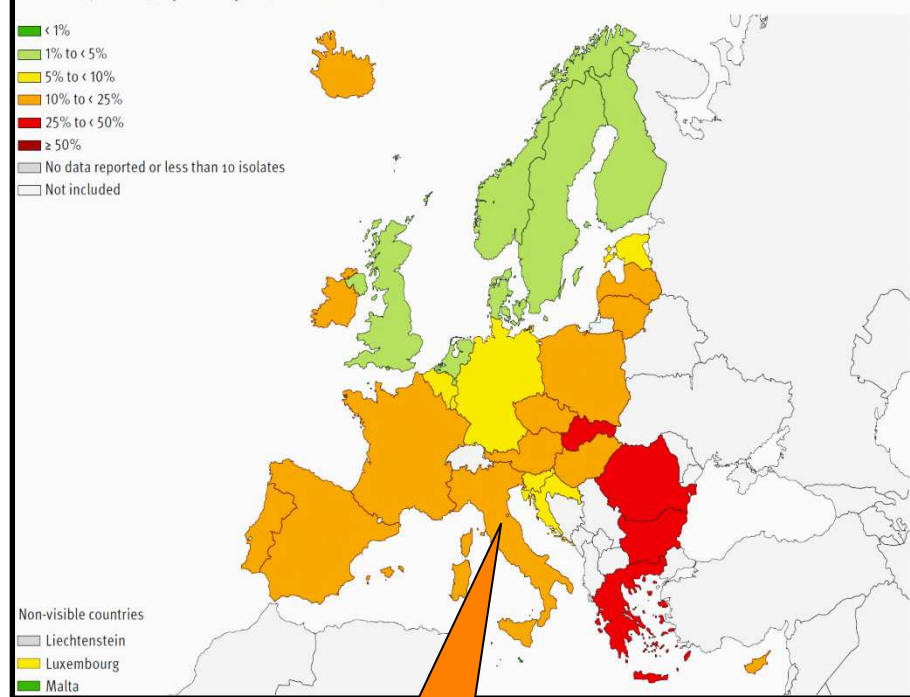
Figure 4.24: *Pseudomonas aeruginosa*: percentage (%) of invasive isolates with combined resistance (resistance to three or more antimicrobial classes among piperacillin (\pm tazobactam), ceftazidime, fluoroquinolones, aminoglycosides and carbapenems), by country, EU/EEA countries, 2011



17.3%

2011

Figure 3.25: *Pseudomonas aeruginosa*. Percentage (%) of invasive isolates with combined resistance (resistance to three or more antimicrobial classes among piperacillin (\pm tazobactam), ceftazidime, fluoroquinolones, aminoglycosides and carbapenems), by country, EU/EEA countries, 2012



23.9%

2012

Pseudomonas aeruginosa

Epidemiologia 2012
UDINE

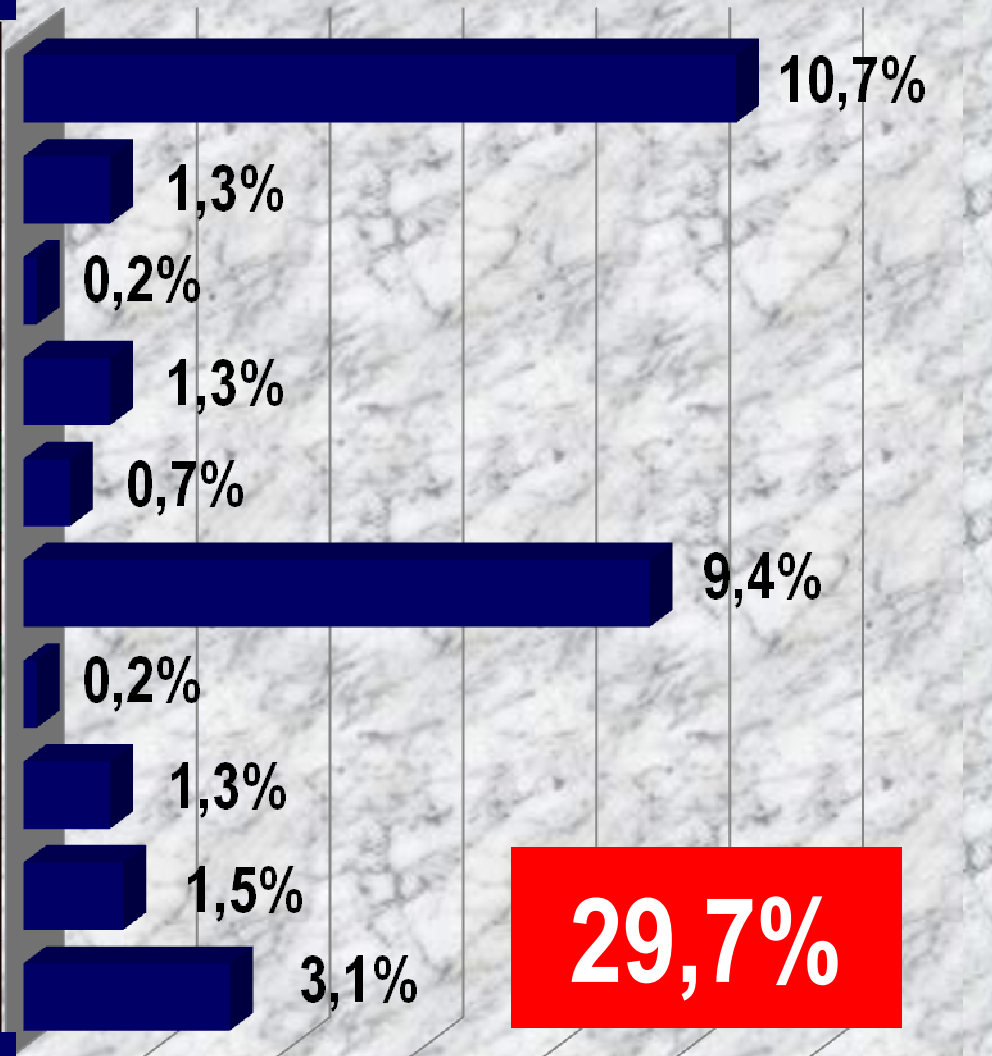
455 isolati da
materiali nobili

Breakpoint
Clinici 2012



FENOTIPO AST

AK: R	CAZ: R	CIP: R	ME: R	P/T: R
AK: R	CAZ: R	CIP: R	ME: S	P/T: R
AK: R	CAZ: R	CIP: S	ME: R	P/T: R
AK: R	CAZ: S	CIP: R	ME: R	P/T: R
AK: R	CAZ: S	CIP: R	ME: R	P/T: S
AK: S	CAZ: R	CIP: R	ME: R	P/T: R
AK: S	CAZ: R	CIP: R	ME: R	P/T: S
AK: S	CAZ: R	CIP: R	ME: S	P/T: R
AK: S	CAZ: R	CIP: S	ME: R	P/T: R
AK: S	CAZ: S	CIP: R	ME: R	P/T: R



Pseudomonas aeruginosa

Epidemiologia 2013
UDINE

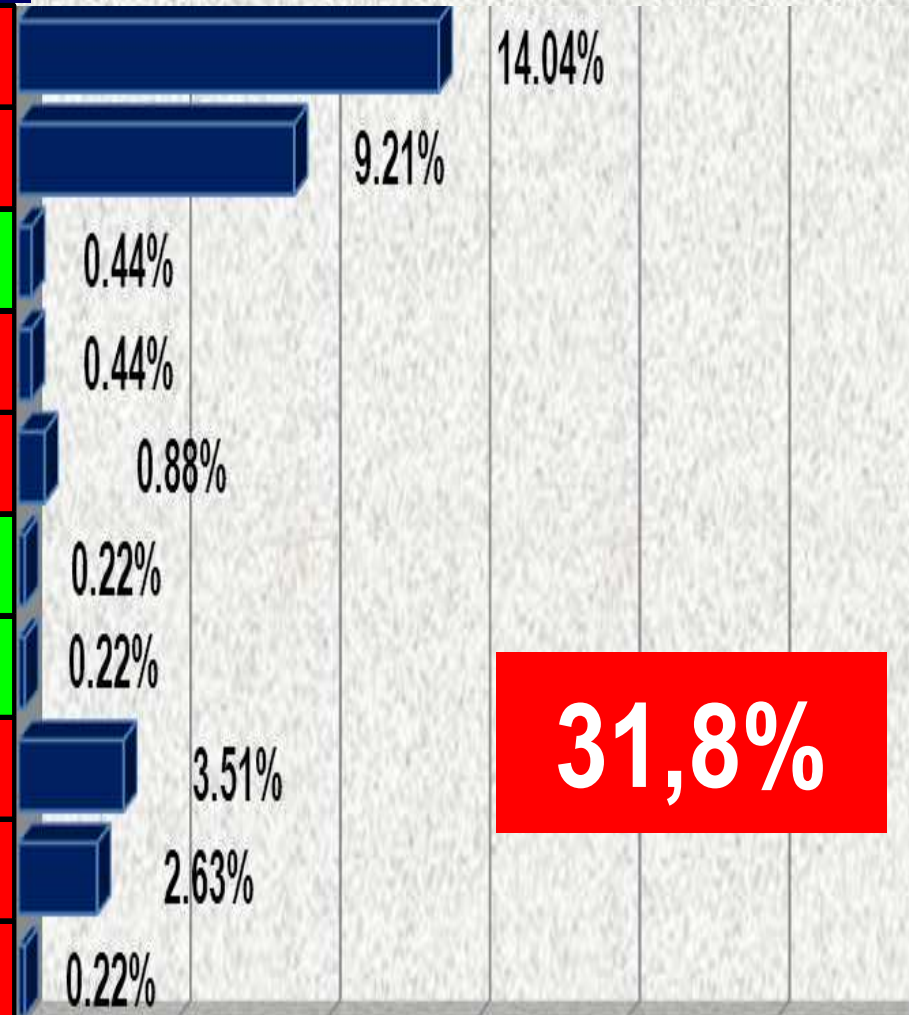
460 isolati da
materiali nobili

Breakpoint
Clinici 2013



FENOTIPO AST

AK: R	CAZ: R	CIP: R	ME: R	P/T: R
AK: S	CAZ: R	CIP: R	ME: R	P/T: R
AK: R	CAZ: R	CIP: R	ME: R	P/T: S
AK: R	CAZ: R	CIP: R	ME: S	P/T: R
AK: R	CAZ: S	CIP: R	ME: R	P/T: R
AK: S	CAZ: R	CIP: R	ME: R	P/T: S
AK: R	CAZ: S	CIP: R	ME: R	P/T: S
AK: S	CAZ: R	CIP: R	ME: S	P/T: R
AK: S	CAZ: S	CIP: R	ME: R	P/T: R
AK: R	CAZ: S	CIP: S	ME: R	P/T: R



ACINETOBACTER BAUMANNII (da materiali nobili)

DISTRIBUZIONE MIC

2013

2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64
TV	AMIKACINA	187	14						3	6	4	1	0	86	
UD	AMIKACINA	20	70						5	20	35	10	0	30	
TV	CIPROFLOXACINA	187	7	5	2	0	0	0	0	0	93				
UD	CIPROFLOXACINA	20	60	30	25	5	0	0	0	0	40				
TV	LEVOFLOXACINA	187	7			7	0	0	0	0	0	93			
UD	LEVOFLOXACINA	20	60			35	5	0	20	0	5	35			
TV	TRIMET/SULFA	187	12				6	1	4	1	1	87			
UD	TRIMET/SULFA	20	60			5	25	30	0	0	5	35			
TV	MEROPENEM	187	11				5	4	2	0	0	0	0	25	64
UD	MEROPENEM	20	60			15	35	5	5	0	0	0	0	15	25
TV	COLISTINA	187	98				30	61	7	0	1	1			
UD	COLISTINA	20	100				25	60	10	5					
2013	Antimicrobico	N. Ceppi	% S	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	64

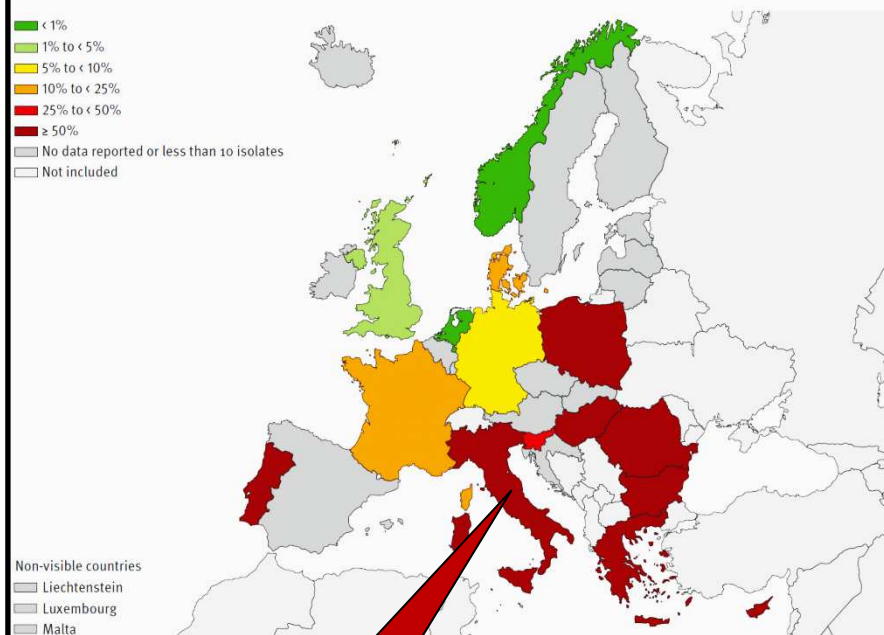
EARS-NET 2012: *Acinetobacter baumannii*

% of invasive isolates with resistance to:

Fluoroquinolones

Aminoglycosides

Figure 3.32. *Acinetobacter* spp. Percentage (%) of invasive isolates with resistance to fluoroquinolones, by country, EU/EEA countries, 2012



86%

UDINE

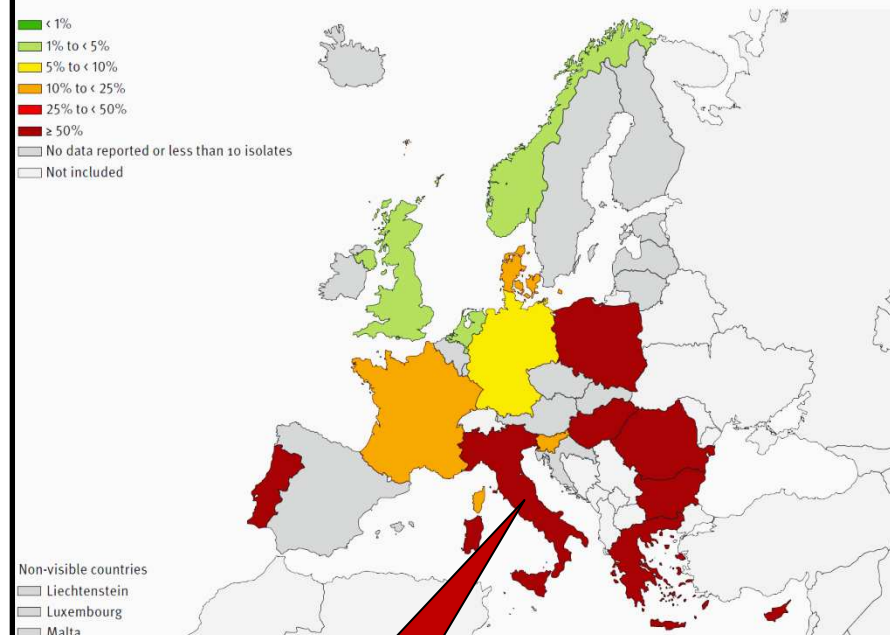
40%

TREVISO

93%

2013

Figure 3.33. *Acinetobacter* spp. Percentage (%) of invasive isolates with resistance to aminoglycosides, by country, EU/EEA countries, 2012



83%

UDINE

30%

TREVISO

86%

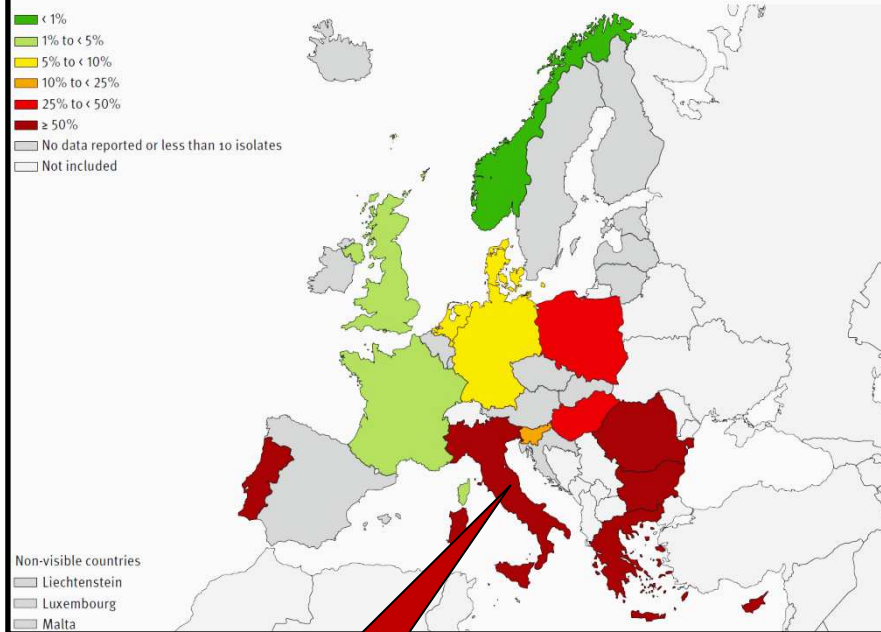
EARS-NET 2012: *Acinetobacter baumannii*

% of invasive isolates with resistance to:

Carbapenems

Fluoroquinolones, Aminoglycosides and Carbapenems (Combined resistance)

Figure 3.34. *Acinetobacter* spp. Percentage (%) of invasive isolates with resistance to carbapenems, by country, EU/EEA countries, 2012



83%

UDINE

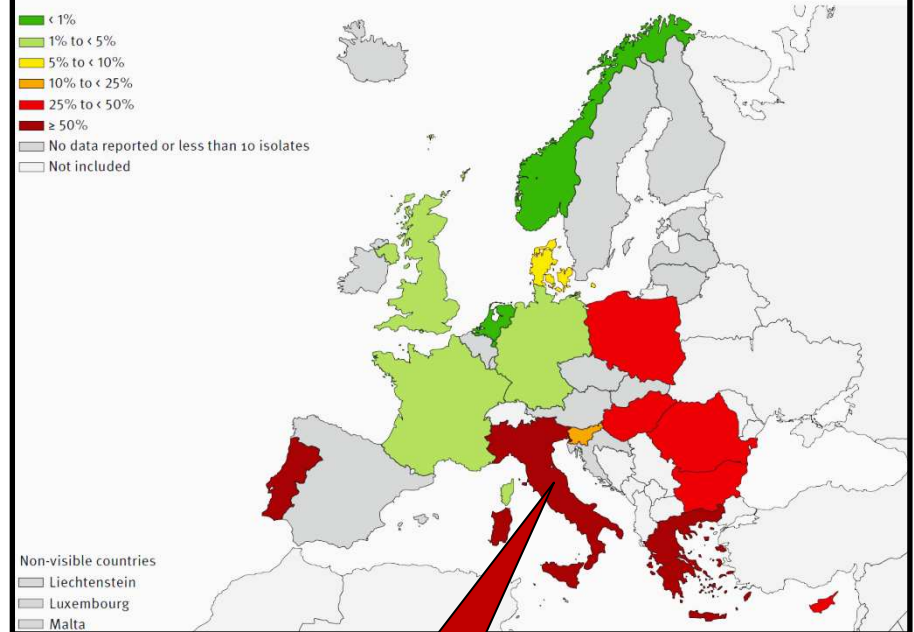
40%

TREVISO

89%

2013

Figure 3.35. *Acinetobacter* spp. Percentage (%) of invasive isolates with combined resistance (resistance to fluoroquinolones, aminoglycosides and carbapenems), by country, EU/EEA countries, 2012



78%

ACINETOBACTER BAUMANNII (da materiali nobili)

DISTRIBUZIONE MIC

2013

2013	Antimicrobico	N. Ceppi	% S	0.12	0.25	0.5	1	2	4	8	16	32	64
PO	MEROPENEM	6	50			17	33					33	17
PO	COLISTINA	6	100			67	33						
VI	MEROPENEM	34	47	3	12	29	0	3	0	0	0	35	18
VI	COLISTINA	34	97		24	41	32	0	3				
CO	MEROPENEM	80	23	7	9	6	0	1	0	0	1	8	68
CO	COLISTINA	80	100		11	69	20						
ME	MEROPENEM	177	21	3	10	2	5	1	1	4	31	32	11
ME	COLISTINA	177	97		30	60	5	2	0	3			
RO	MEROPENEM	93	6		3	2	1	0	0	2	38	28	26
RO	COLISTINA	93	97		27	50	20	0	0	3			
2013	Antimicrobico	N. Ceppi	% S	0.12	0.25	0.5	1	2	4	8	16	32	64

Acinetobacter baumannii

Epidemiologia 2012
UDINE

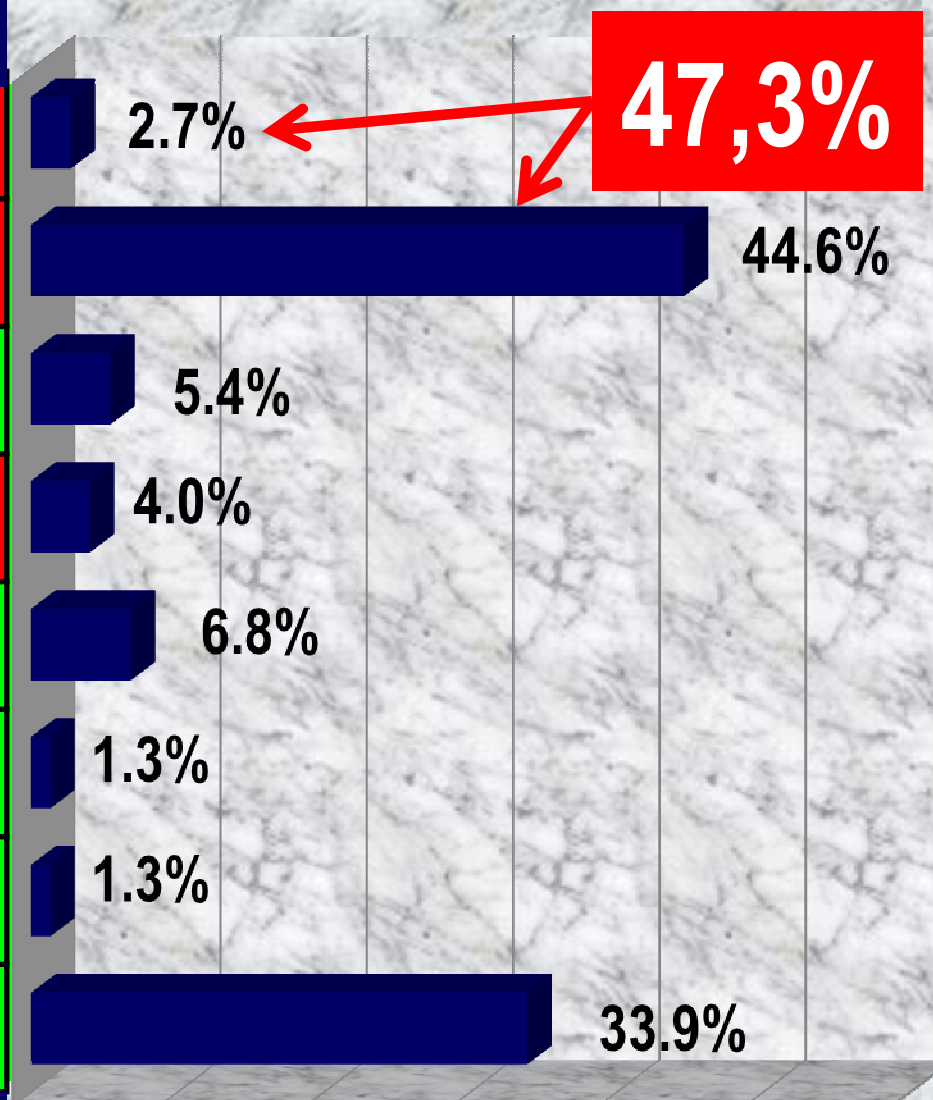
51 isolati da
materiali nobili

Breakpoint
Clinici 2012



FENOTIPO AST

AK: R	CIP: R	COL: R	LEV: R	ME: R
AK: R	CIP: R	COL: S	LEV: R	ME: R
AK: R	CIP: R	COL: S	LEV: R	ME: S
AK: S	CIP: R	COL: S	LEV: R	ME: R
AK: S	CIP: R	COL: S	LEV: R	ME: S
AK: S	CIP: S	COL: R	LEV: S	ME: S
AK: R	CIP: S	COL: S	LEV: S	ME: S
AK: S	CIP: S	COL: S	LEV: S	ME: S



Acinetobacter baumannii

Epidemiologia 20123
UDINE

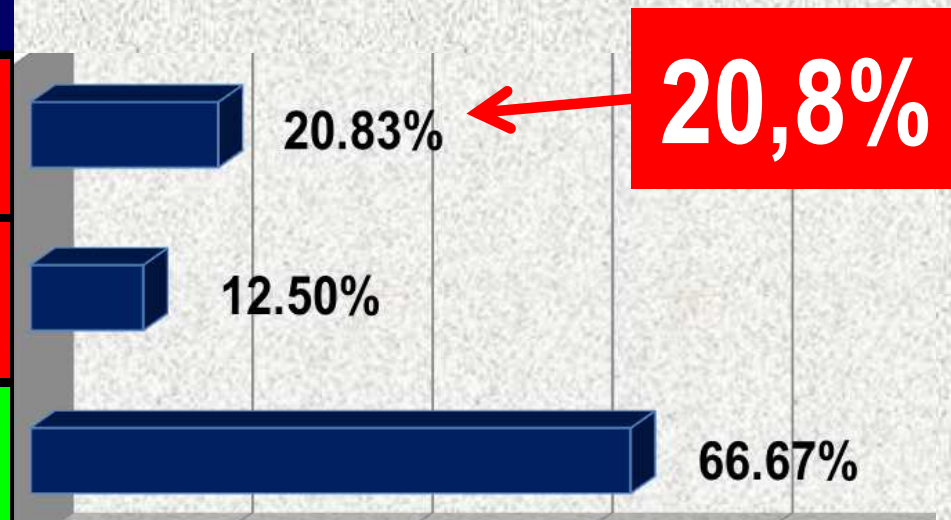
20 isolati da
materiali nobili

Breakpoint
Clinici 2013



FENOTIPO AST

AK: R	CIP: R	COL: S	LEV: R	ME: R
AK: S	CIP: R	COL: S	LEV: R	ME: R
AK: S	CIP: S	COL: S	LEV: S	ME: S



Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution

Roberts JA, et al. J Antimicrob Chemother 2009; 64:142:150

Table 3. CFR (%) for meropenem on day 1 of treatment for Gram-negative pathogens for various intermittent bolus, extended and continuous dosing strategies of meropenem in critically ill patients with sepsis

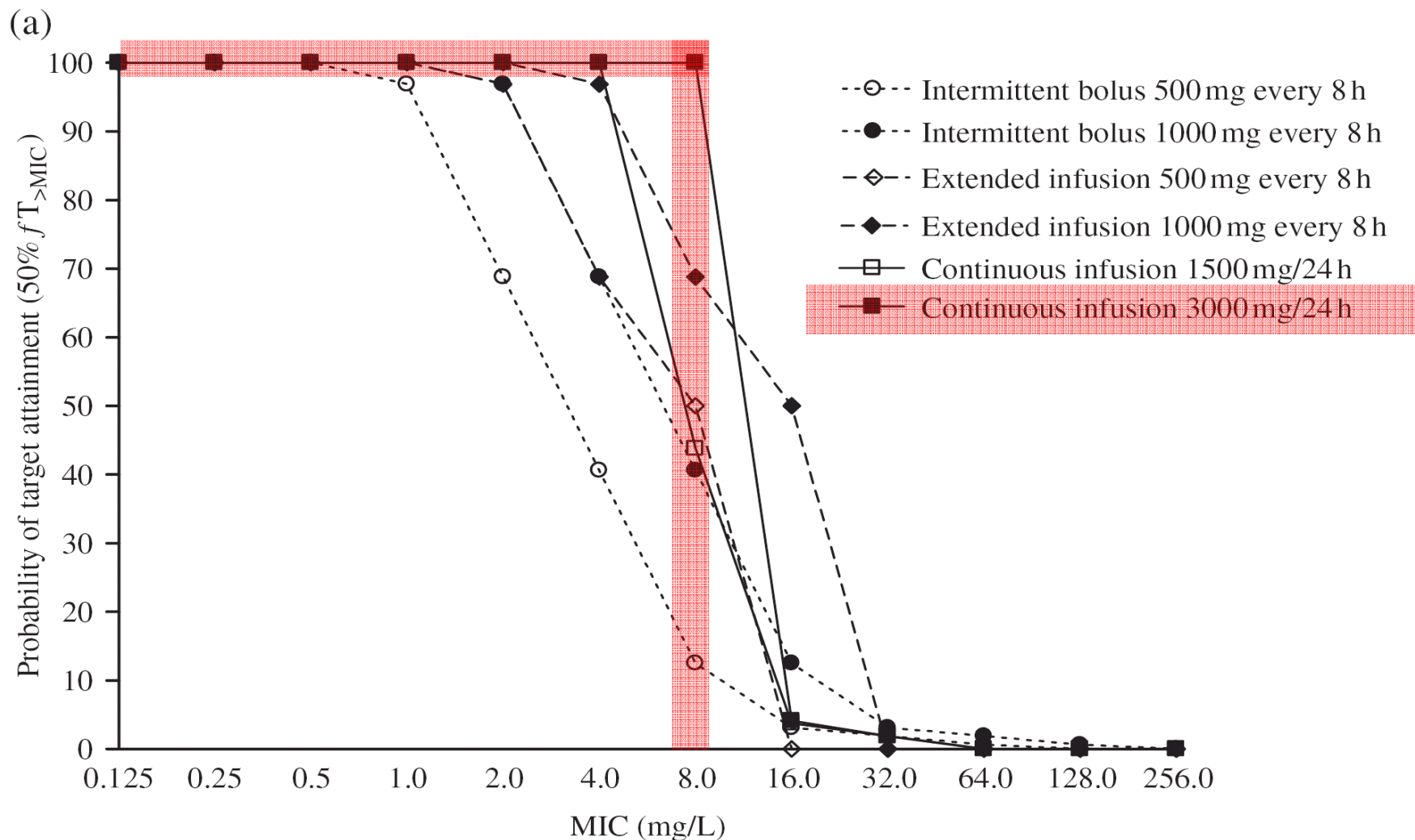
Organism	MIC ₉₀ (mg/L)	Intermittent bolus dosing			Extended infusion			Continuous infusion		
		500 mg 8 hourly	1000 mg 8 hourly	2000 mg 8 hourly	500 mg 8 hourly	1000 mg 8 hourly	2000 mg 8 hourly	1500 mg/day	3000 mg/day	6000 mg/day
<i>E. coli</i>	0.06	100	100	100	100	100	100	100	100	100
<i>K. pneumoniae</i>	0.06	100	100	100	100	100	100	100	100	100
<i>Enterobacter</i> sp.	0.12	100	100	100	100	100	100	100	100	100
<i>S. marcescens</i>	0.12	100	100	100	100	100	100	100	100	100
<i>Citrobacter</i> sp.	0.12	100	100	100	100	100	100	100	100	100
<i>P. aeruginosa</i>	8	12.5	40.6	68.8	50	68.8	96.9	43.8	100	100
<i>Acinetobacter</i> sp.	16	3.1	12.5	40.6	0	50	68.8	3.8	4.1	100

MIC₉₀, minimum inhibitory concentration for 90% of tested strains. The target chosen was 40% $fT_{>MIC}$. Susceptibility data obtained from the 2004–05 MYSTIC surveillance programme in the USA.^{21,22}

For treatment of less-susceptible *P. aeruginosa* and *Acinetobacter* species, administration by extended or continuous dosing may be clinically advantageous due to superior achievement of target exposures, particularly in critically ill patients with sepsis and without renal dysfunction.

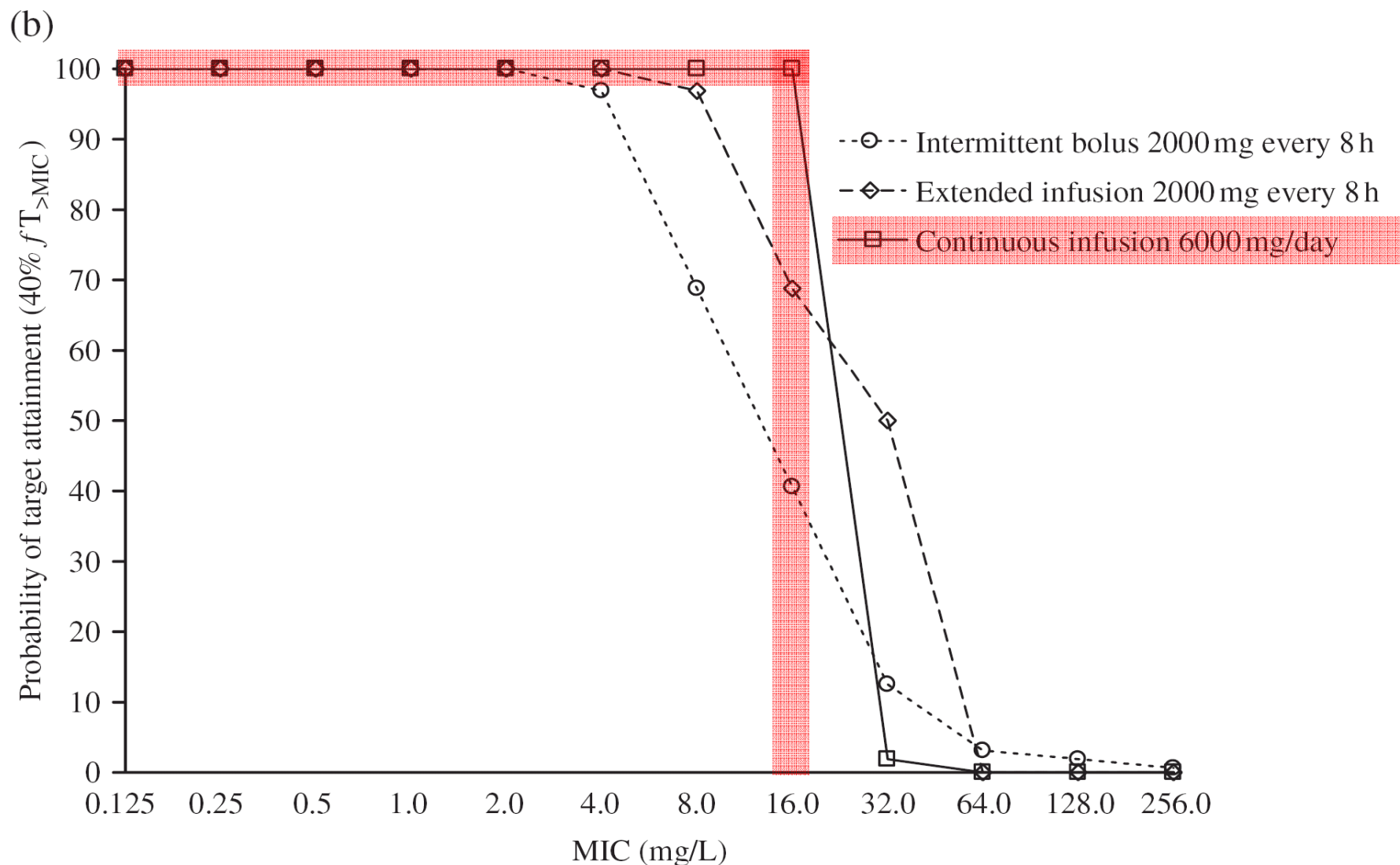
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Continuous Infusion of Beta-Lactam Antibiotics in Severe Sepsis: A Multicenter Double-Blind, Randomized Controlled Trial

Joel M. Dulhunty,¹ Jason A. Roberts,¹ Joshua S. Davis,² Steven A. R. Webb,³ Rinaldo Bellomo,⁴ Charles Gomersall,⁵ Charudatt Shirwadkar,⁶ Glenn M. Eastwood,⁴ John Myburgh,⁷ David L. Paterson,⁸ and Jeffrey Lipman¹

Ellie J. C. Goldstein, Section Editor

Clinical Outcomes With Extended or Continuous Versus Short-term Intravenous Infusion of Carbapenems and Piperacillin/Tazobactam: A Systematic Review and Meta-analysis

Matthew E. Falagas,^{1,2,4} Giannoula S. Tansarli,¹ Kazuro Ikawa,³ and Konstantinos Z. Vardakas^{1,2}

A collection of approximately 15 colored pencils of various colors (including blue, green, yellow, red, black, orange, and grey) are arranged in a circle on a white surface, with their tips pointing towards the center. The pencils are of different colors and some are sharpened.

**GRAZIE PER
L'ATTENZIONE**