TERAPIA DELLE INFEZIONI DA MICRORGANISMI MULTIRESISTENTI

Università degli Studi di Verona

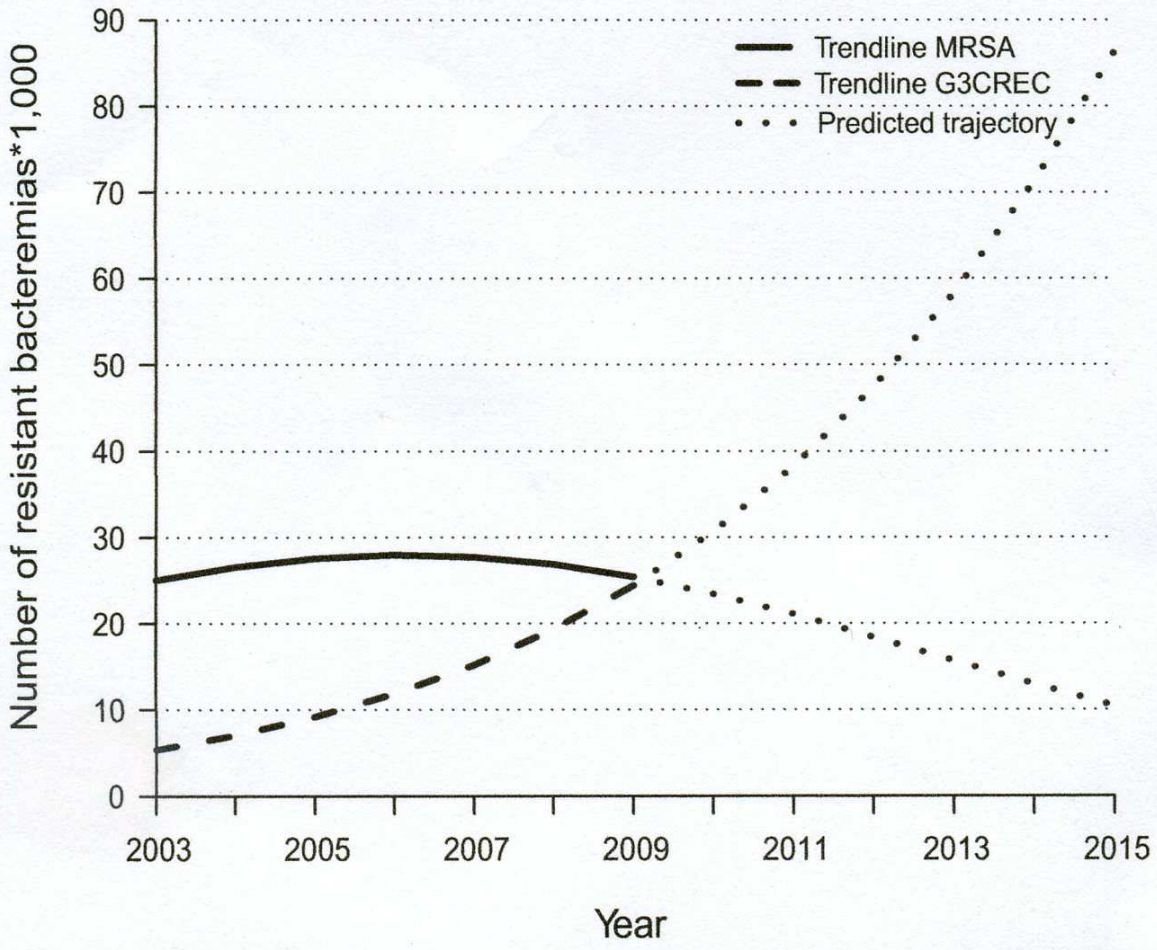
Prof. Ercole Concia

Quali le problematiche, oggi emergenti in antibioticoterapia?

- Aumento delle resistenze batteriche (MDR-PDR-XDR)
- Riduzione marcata della ricerca e sviluppo di nuovi antibiotici

- *Gli antibiotici sono oggi quasi tutti generici: quali le problematiche*
- *Le categorie omogenee*
- *Le prescrizioni off label*
- *I nuovi antibiotici e antifungini*

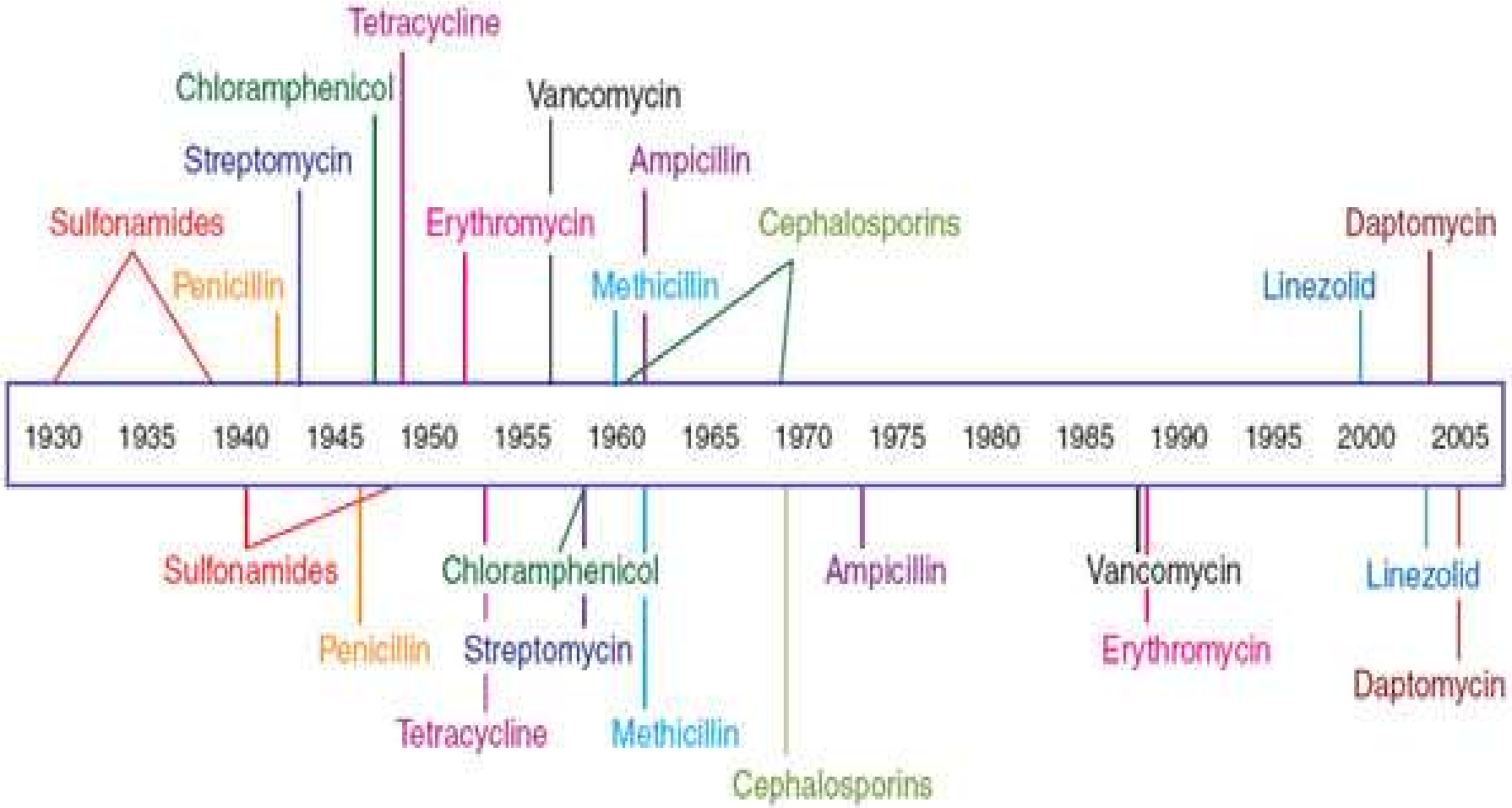
GRAM -



MRSA

Figure 1. Trends in the estimated number of MRSA and G3CREC bacteremias in the European region. Extrapolated EARSS numbers for 2003–2009, and future trajectories based on regression analysis for 2010–2015.
doi:10.1371/journal.pmed.1001104.g001

Antibiotic deployment

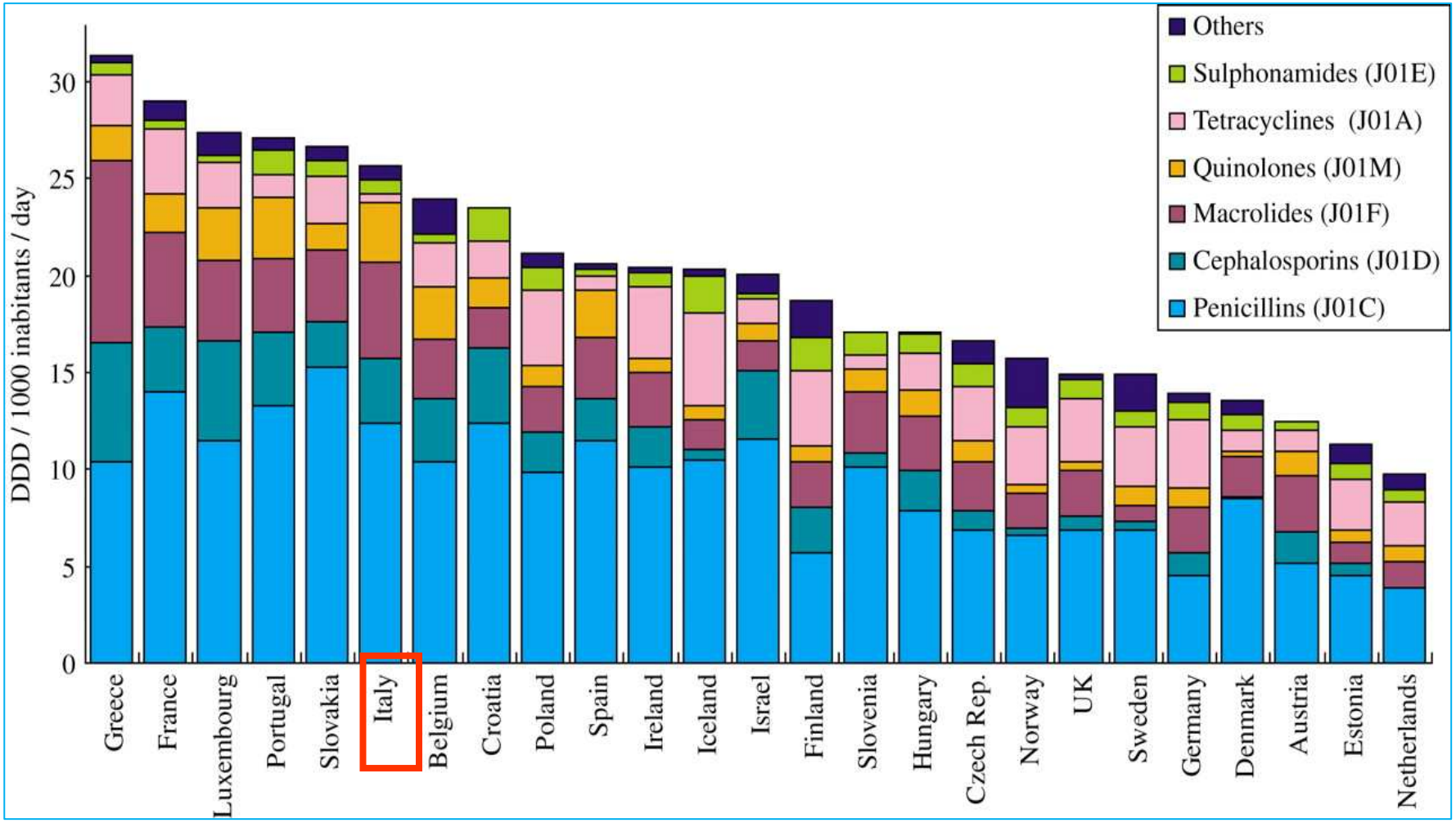


Antibiotic resistance observed

Pazienti sottoposti a terapia antibiotica in ospedale

	%	
PIEMONTE	**36.5**	
VENETO	**50.8**	
TOSCANA	**51**	49% terapia 46% profilassi 5% non noto
PUGLIA	**52**	
CALABRIA	**40**	
SVIZZERA	**24.4**	
INGHILTERRA	**33**	
FRANCIA	**25.5**	

(Privitera 2007)



Total outpatient antibiotic use in 25 European countries in 2003. Cephalosporins includes monobactams and carbapenems; macrolides includes lincosamides and streptogramins; sulphonamides includes trimethoprim; and others includes J01B, J01G, J01R and J01X. For Iceland total data are used; for Poland 2002 data are used.

JAC

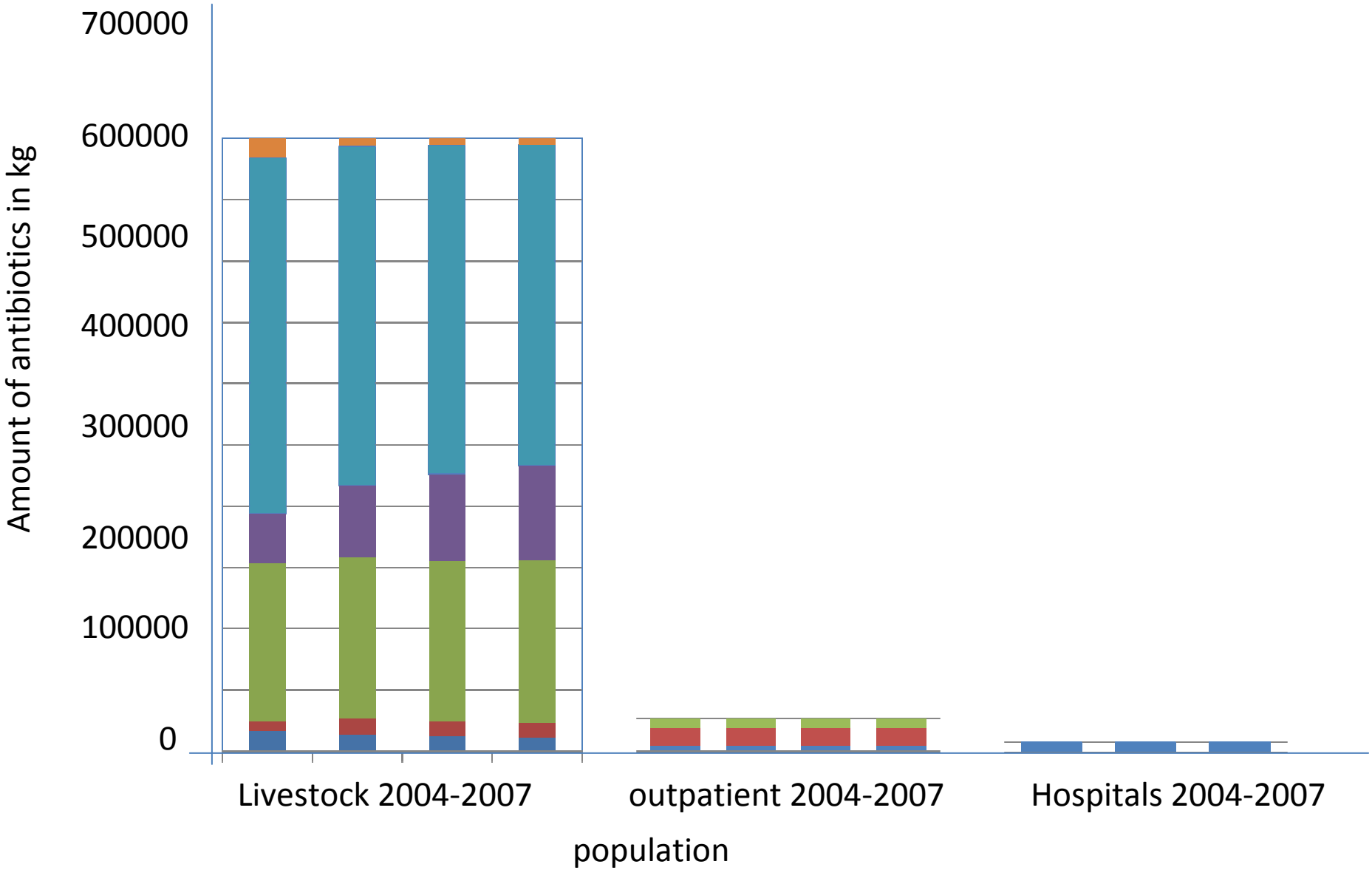
Ferech, M. et al. J. Antimicrob. Chemother. 2006 58:401-407; doi:10.1093/jac/dkl188

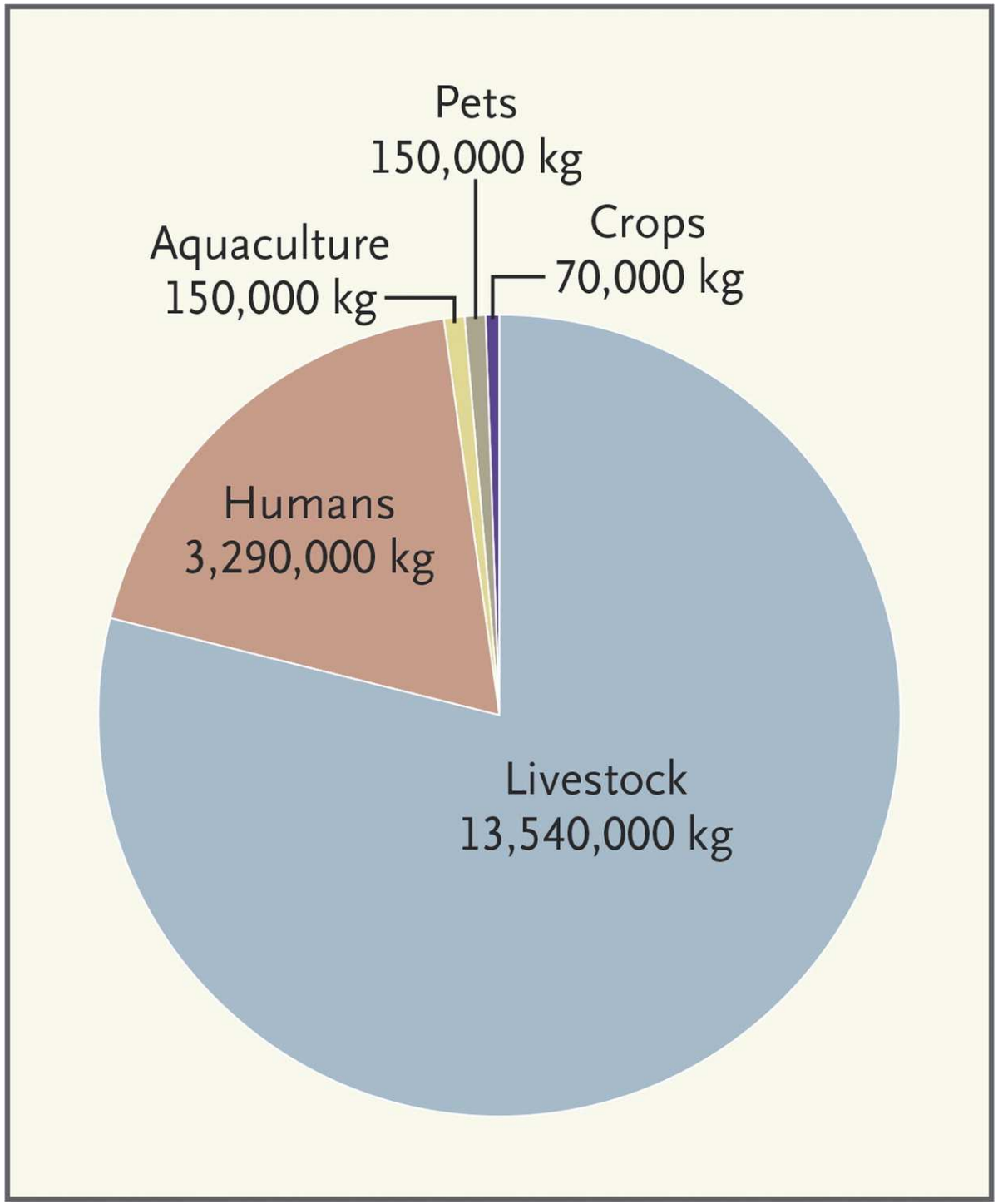
USE OF ANTIBIOTICS

Where antibiotics Are used	Types of use	Questionable use
Human use (50%)	**20% Hospital 80% Community**	**20-50% Unnecessary**
Agricultural use (50%)	**20% Therapeutic 80% Prophylactic /growth promotion**	**40-80% Highly questionable**

P.F Harrison 1998

Humans versus animals in kilograms
The Netherlands 2004-2007

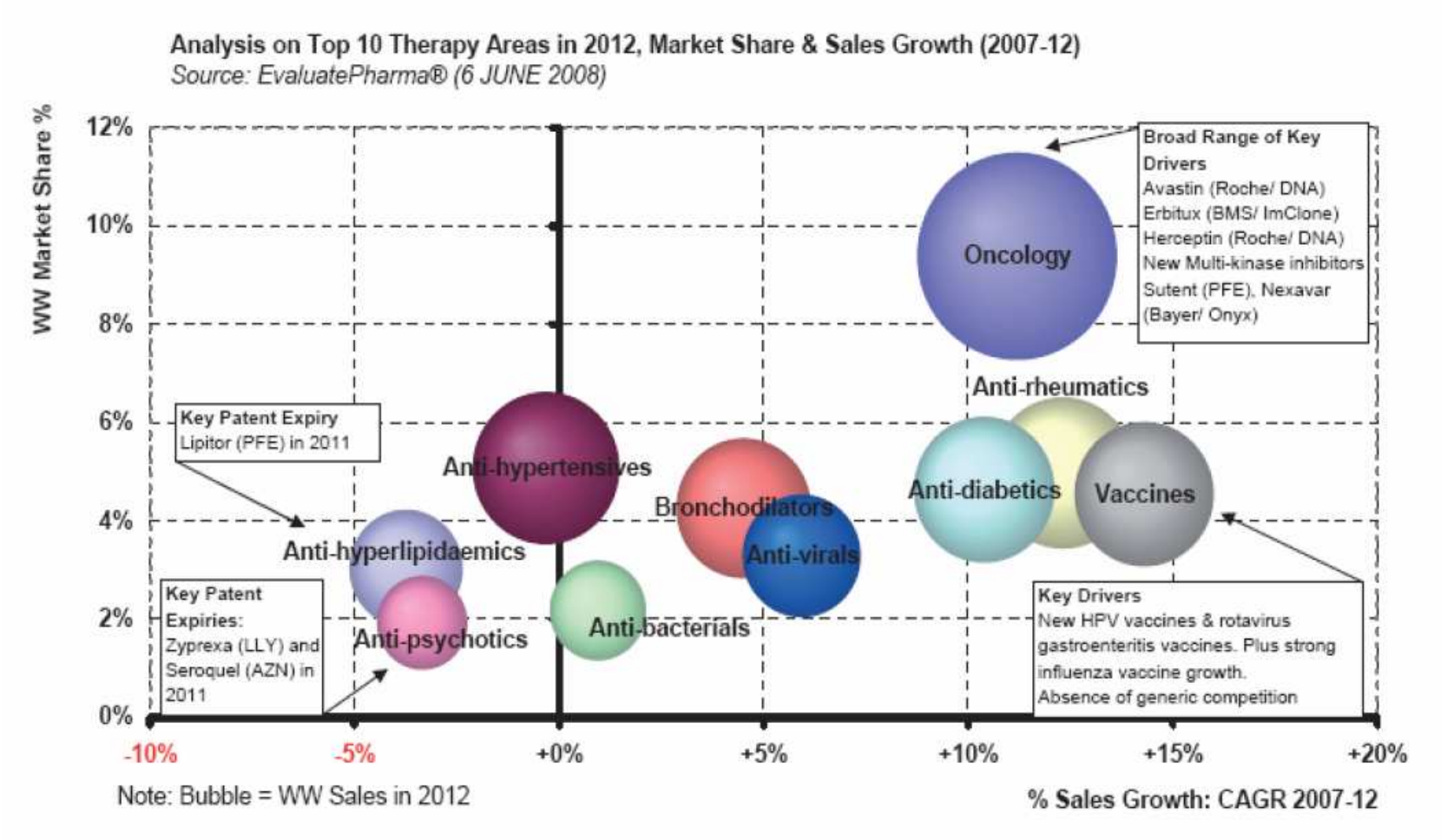



Pets
150,000 kg
Crops
70,000 kg
Aquaculture
150,000 kg
Humans
3,290,000 kg
Livestock
13,540,000 kg

Percentuali di resistenza riscontrate nei POLLI

AMPICILLINA	73
CEFOTAXIME	19
GENTAMICINA	62
STREPTOMICINA	65
TETRACICLINE	62
TRIMETOPRIM	65
CIPROFLOXACINA	58
CLORAMFENICOLO	25
COLISTINA	0

Aree Terapeutiche nel 2012



World Preview 2012

Table 2. Antibacterial Pipeline (Anti–Gram Positive and Anti–Gram Negative), Big Pharma

Company	Since 1998	Phase 2/3
Abbott Laboratories	0	0
AstraZeneca	0	2
Bayer	0	0
GlaxoSmithKline	0	1
Lilly	0	0
Merck/Schering-Plough	1	1
Novartis	0	0
Ortho McNeil/Johnson & Johnson	1	0
Pfizer/Wyeth	2	0
Roche	0	0
Sanofi	0	0

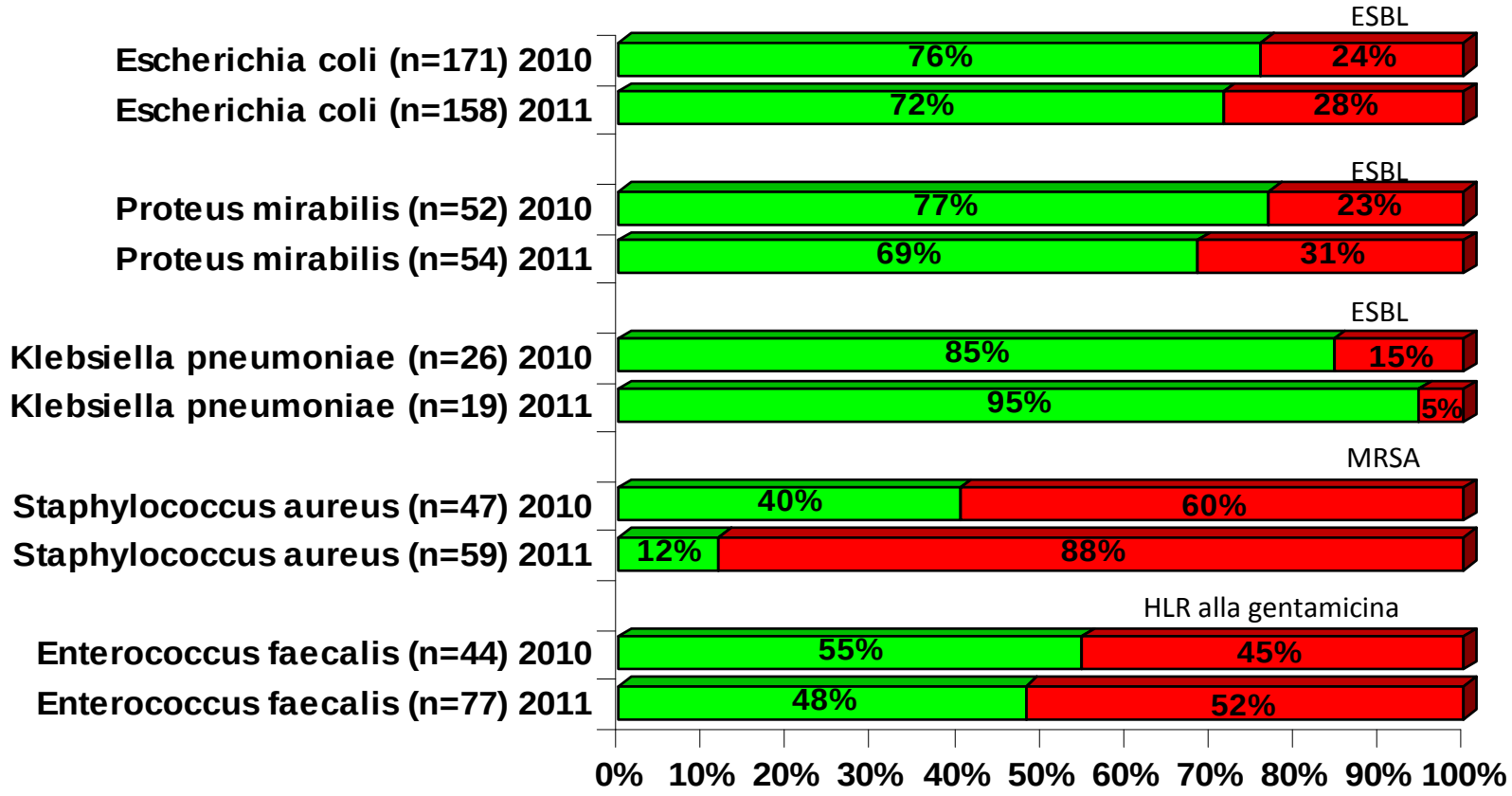
NUOVI SCENARI: RSA O LUNGODEGENZE PER ANZIANI

Tavola 1.1 - Presidi residenziali socio-assistenziali e socio-sanitari, posti letto, ospiti per tipologia di utenza e Regione presenti il 31 dicembre 2009 (valori assoluti)

REGIONE	Presidi residenziali	Totale posti letto	Ospiti				
			Minori	Adulti	Anziani autosufficienti	Anziani non autosufficienti	Totale
Piemonte	1.251	43.485	1.178	5.397	12.680	23.599	42.854
Valle d'Aosta/Vallée d'Aoste	60	1.274	18	202	98	894	1.212
Liguria	498	16.400	526	2.339	3.972	7.113	13.950
Lombardia	2.385	105.677	3.701	20.148	7.231	71.075	102.155
Trentino-Alto Adige/Südtirol	431	12.732	510	3.483	867	7.459	12.319
Bolzano-Bozen	*193*	*6.123*	*166*	*2.073*	*447*	*3.348*	*6.034*
Trento	*238*	*6.609*	*344*	*1.410*	*420*	*4.111*	*6.285*
Veneto	1.032	46.621	1.491	6.373	6.644	30.429	44.937
Friuli-Venezia Giulia	362	13.525	298	1.693	2.396	8.947	13.334
Emilia-Romagna	1.526	42.436	1.959	7.151	4.829	24.162	38.101
Toscana	804	24.029	1.124	4.100	5.462	12.402	23.088
Umbria	174	4.086	212	1.313	623	1.893	4.040
Marche	394	11.509	424	1.816	1.825	5.242	9.306
Lazio	1.028	25.453	2.078	5.092	8.069	7.373	22.613
Abruzzo	266	10.139	270	1.668	2.982	4.739	9.659
Molise	80	2.947	93	845	781	954	2.672
Campania	712	8.706	2.378	2.368	2.428	900	8.074
Puglia	474	13.434	1.042	3.198	3.249	4.803	12.293
Basilicata	74	2.037	99	701	494	703	1.997
Calabria	335	6.824	877	1.761	1.651	2.259	6.548
Sicilia	1.024	30.372	3.857	9.247	7.115	7.741	27.960
Sardegna	297	7.535	449	1.643	2.473	2.493	7.059
Nord Ovest	4.194	166.835	5.423	28.085	23.982	102.682	160.172
Nord Est	3.351	115.314	4.258	18.700	14.735	70.998	108.691
Centro	2.400	65.076	3.837	12.321	15.978	26.910	59.046
Sud	1.941	44.087	4.760	10.541	11.585	14.357	41.242
Isole	1.321	37.907	4.306	10.890	9.589	10.234	35.019
ITALIA	13.207	429.220	22.584	80.536	75.868	225.182	404.170

RSA della Provincia di Lecco

Specie microbiche isolate da pazienti residenti in 26 RSA nel 2010 e 2011



Dati non pubblicati, per gentile concessione di di F. Luzzaro, marzo 2012

Stafilococco Aureo Meticillino Resistente

MRSA

Figure 5.8: ***Staphylococcus aureus*: proportion of invasive isolates resistant to meticillin (MRSA) in 2010**

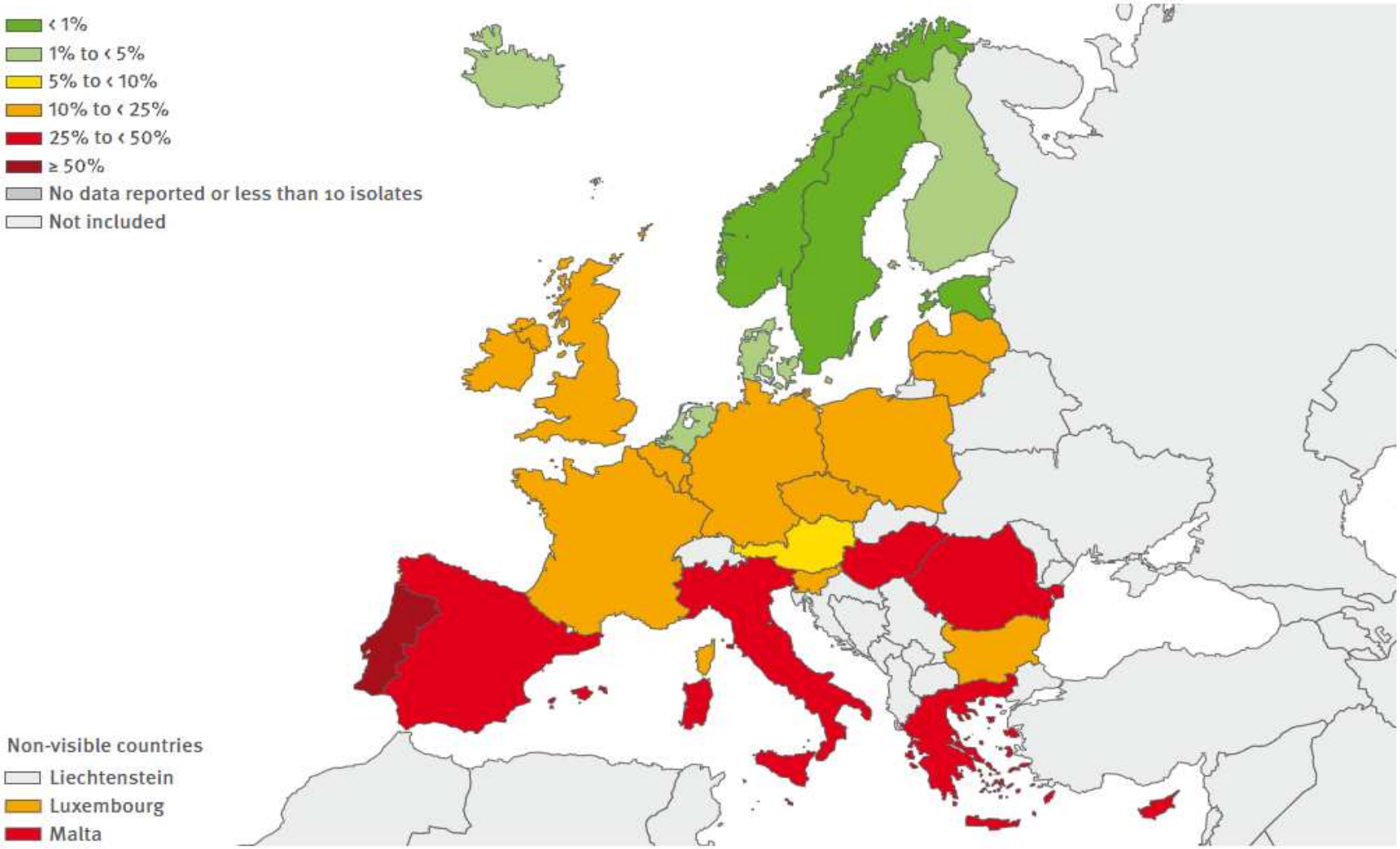


Table 5.3: **Number and proportion of invasive *S. aureus* isolates resistant to meticillin (MRSA) and rifampin (RIF), including 95% confidence intervals (95% CI), reported per country in 2010**

Figure 5.8: *Staphylococcus aureus*: proportion of invasive isolates resistant to meticillin (MRSA) in 2010

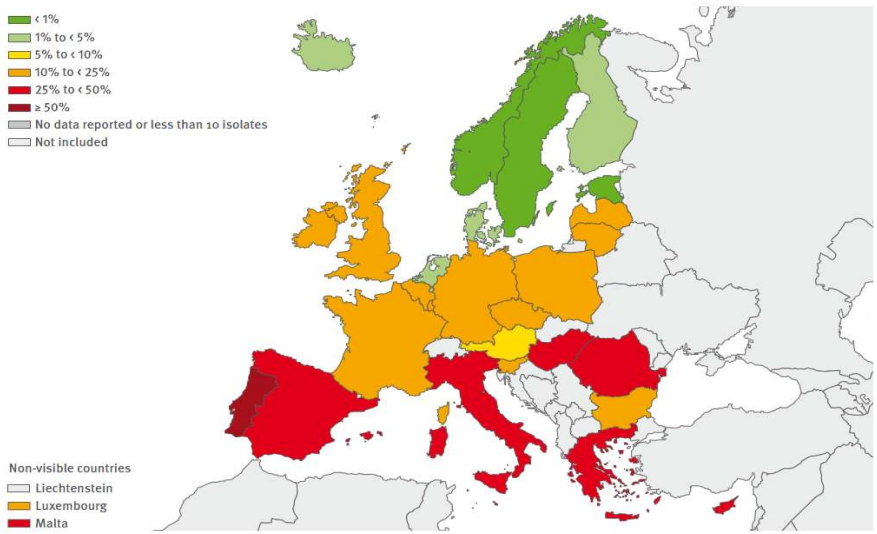


Table 5.3: Number and proportion of invasive *S. aureus* isolates resistant to meticillin (MRSA) and rifampin (RIF), including 95% confidence intervals (95% CI), reported per country in 2010

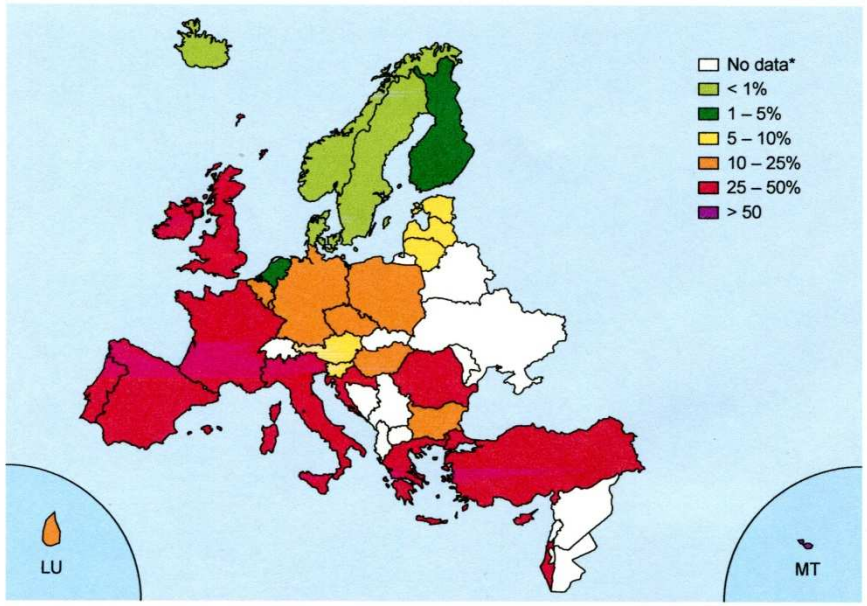
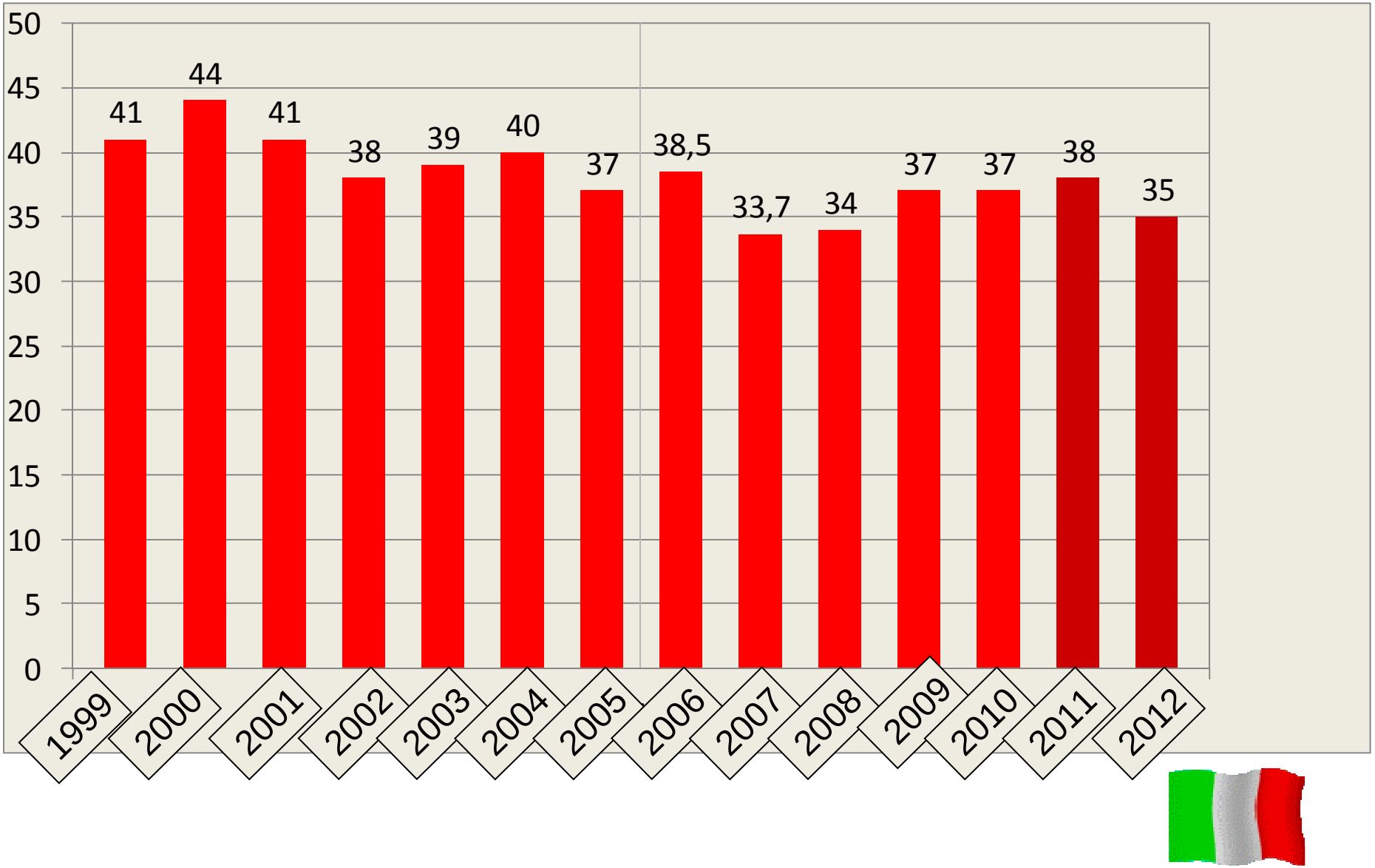


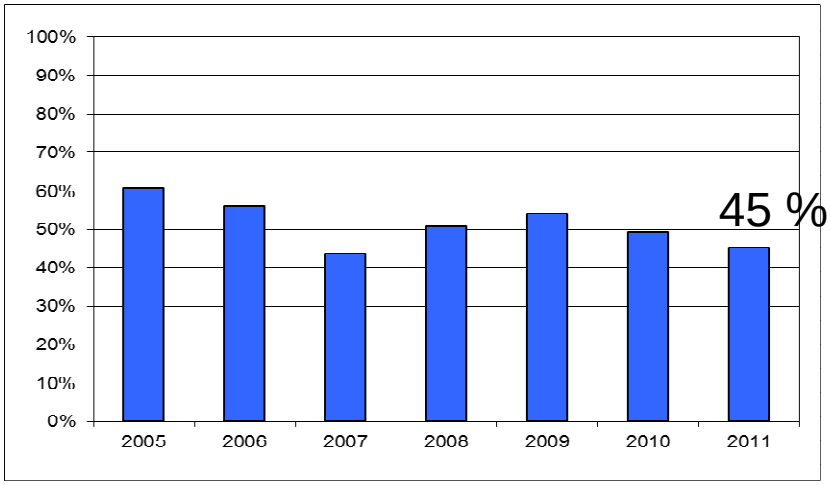
Figure 4.8. *Staphylococcus aureus*: proportion of invasive isolates resistant to oxacillin (MRSA) in 2007.
* These countries did not report any data or reported less than 10 isolates.

Rate of invasive MRSA in Italy: 1999-2010

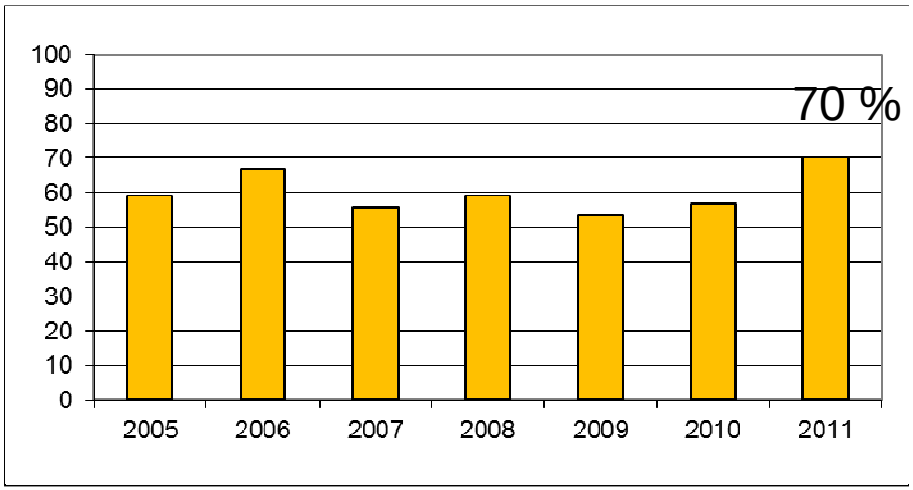


Frequenza dei ceppi di S. aureus meticillino-resistente in Terapia Intensiva vs Geriatria

Terapia Intensiva



Geriatrie



Vancomycin MIC "creep" – USA data

	number	MIC_{50}	MIC_{90}	N(%) MIC > 1.0
1985 MSSA	30	0.06	0.12	1/30 (3)*
2004 MSSA	25	2.0	2.0	25/25 (100)*
1985 MRSA	25	0.12	0.25	2/25 (8)*
2004 MRSA	28	2.0	2.0	25/28 (89)*

* P< 0.0001 - Kapadia M. et al 45° ICAAC abs E-807

MIC per vancomicina e % di eradicazione

TABLE 2. Vancomycin MIC versus eradication rates

Vancomycin MIC (μg/ml)	No. of isolates	Median DTE[a]	Median duration of vancomycin therapy (days)	Eradication rate by EOT[b]	Median reduction in $\log_{10}$ CFU/ml
0.5	13	6.0	13.0	10/13 (77)	3.06
1.0	7	9.5	17.0	5/7 (71)	3.09
2.0	14	>15.0[c]	18.5	3/14 (21)	2.75

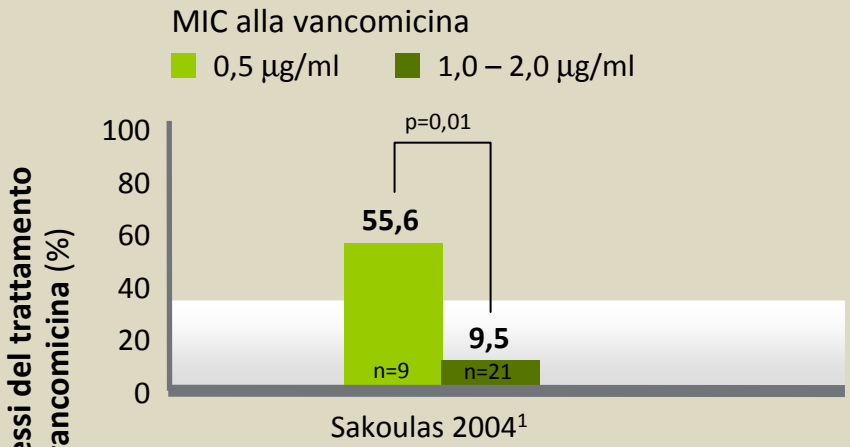
[a] DTE, day to eradication.

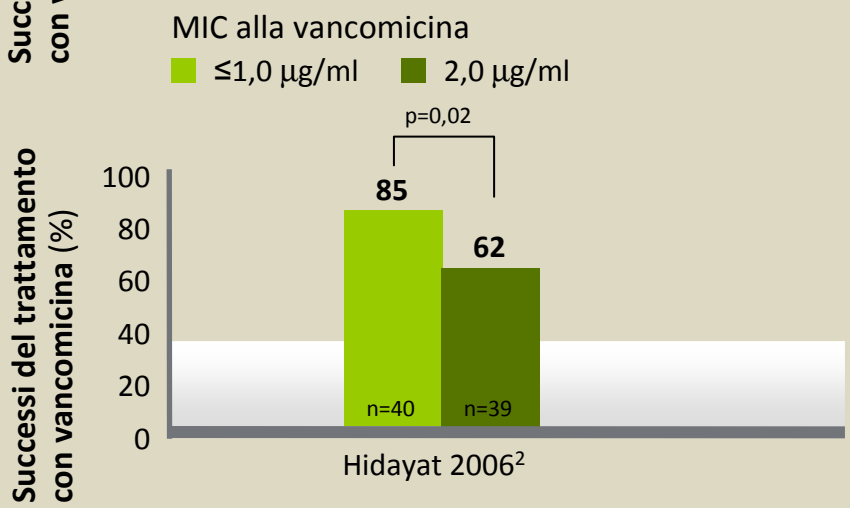
[b] EOT, end of treatment. The eradication rate data represent the number of patients from the organism was eradicated/total number of patients in the group (percent).

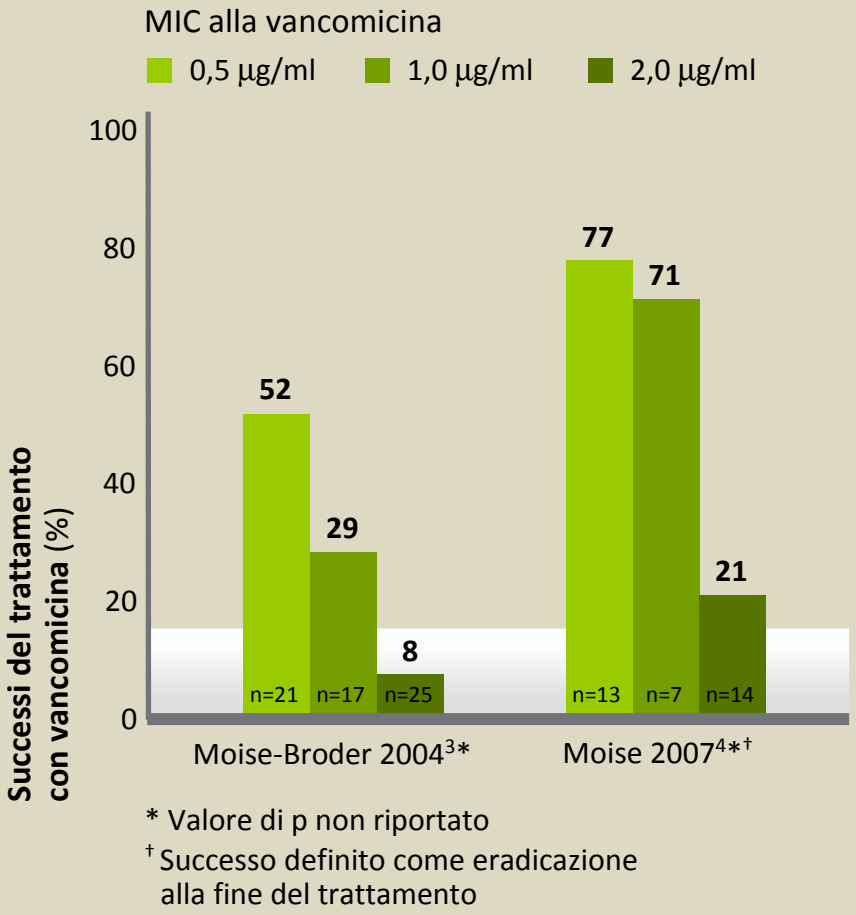
[c] The median time to eradication is greater than 15 days, as only 21% of patients showed clearance of bacteremia.

Moise et al – AAC 2007

La MIC alla vancomicina è un fattore predittivo significativo di fallimento terapeutico nelle infezioni da MRSA







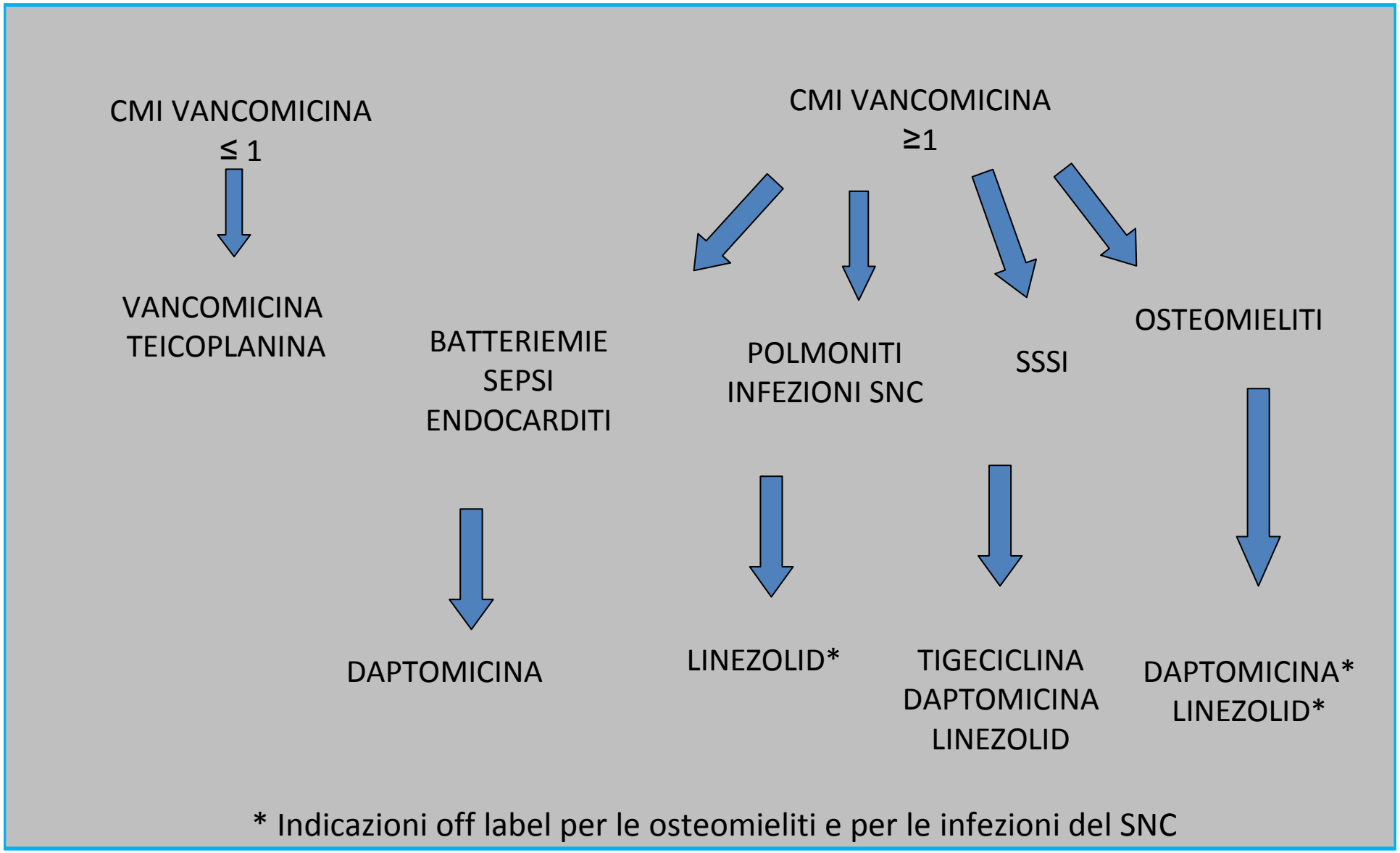
* Valore di p non riportato

† Successo definito come eradicazione alla fine del trattamento

1. Sakoulas G, et al. *J Clin Microbiol* 2004; 42:2398-2402
2. Hidayat L, et al. *Arch Intern Med* 2006; 166:2138-2144

1. Moise-Broder P, et al. *Clin Infect Dis* 2004; 38:1700-1705
2. Moise P, et al. *Antimicrob Agents Chemother* 2007; 51:2582-2586

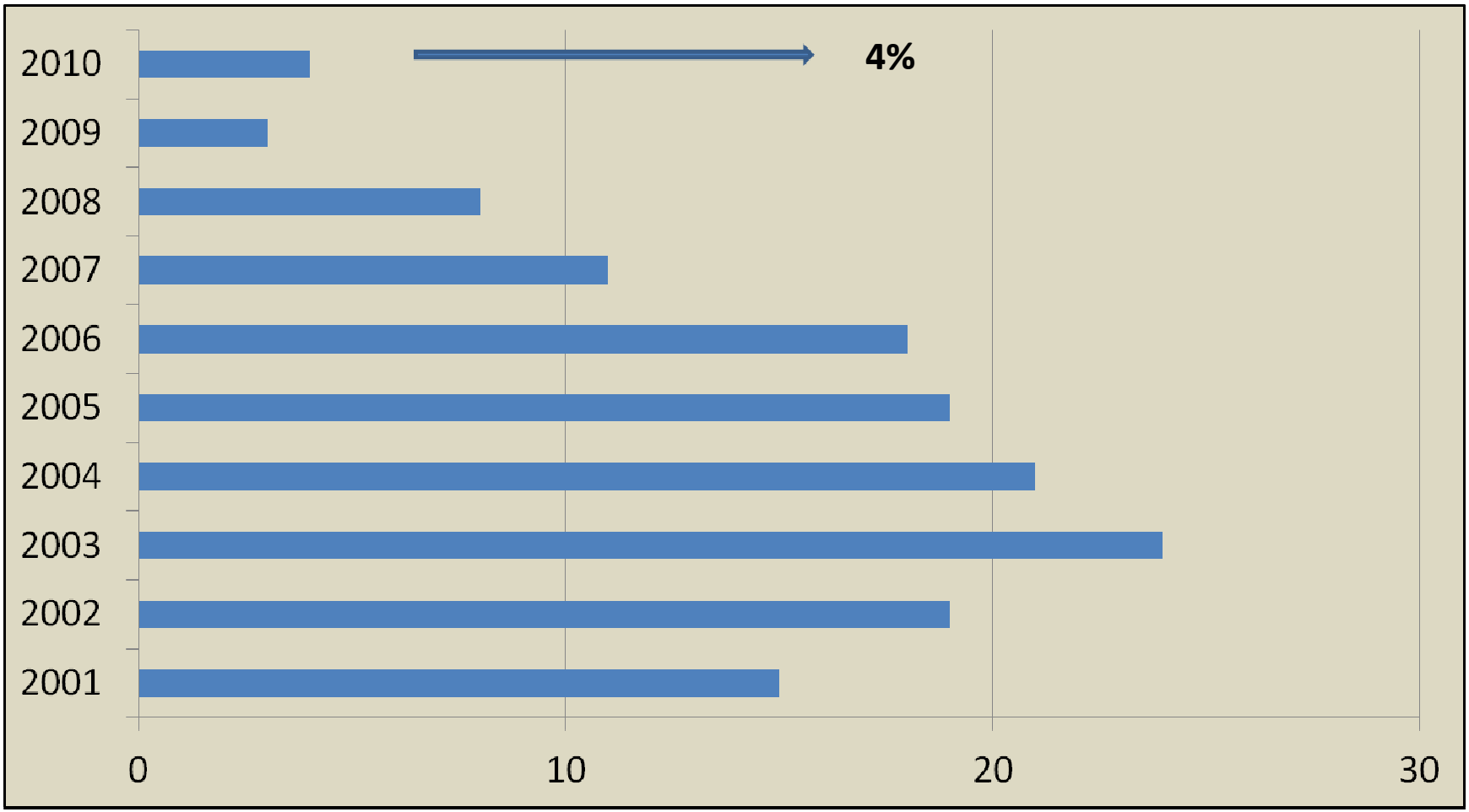
TERAPIA DELLE INFEZIONI DA MRSA
(nelle infezioni da MSSA la terapia d'elezione è l'oxacillina)



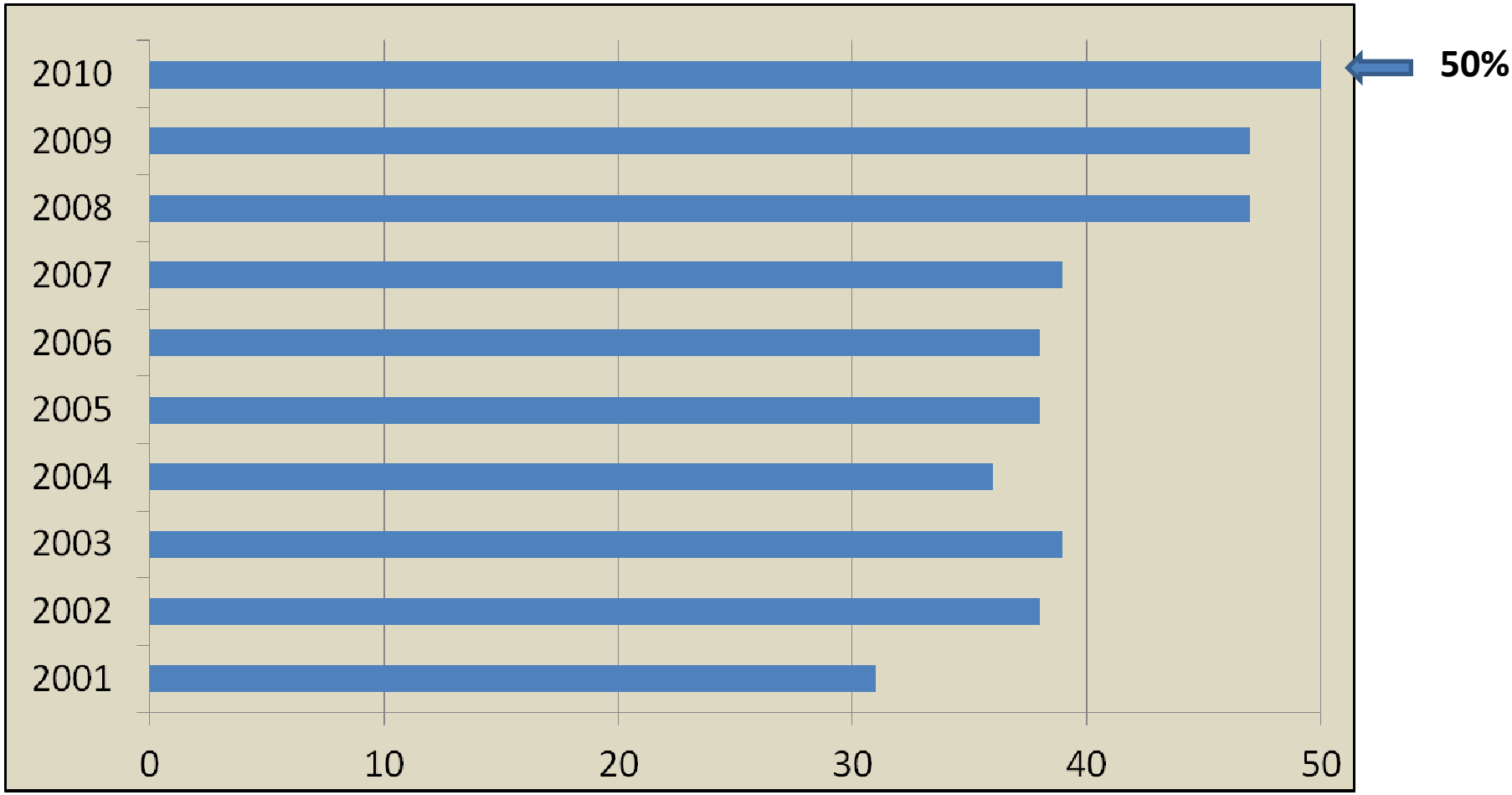
* Indicazioni off label per le osteomieliti e per le infezioni del SNC

ENTEROCOCCHI

VRE (E. *faecium* resistente alla vancomicina)

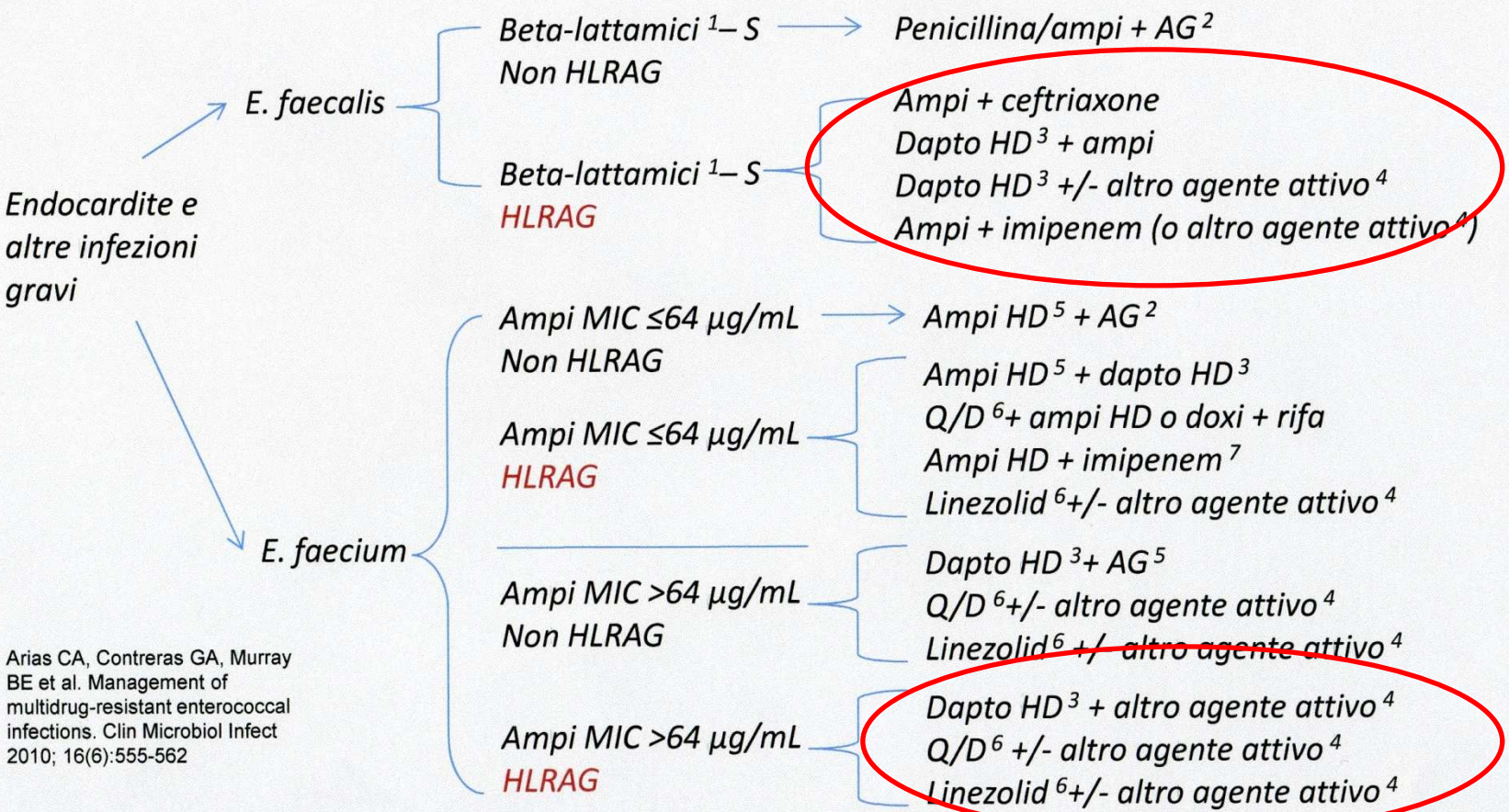


Enterococchi resistenti agli aminosidi



Ampi-S	**Ampicillina**, Vancomicina, Linezolid, Daptomicina, Tigeciclina
Ampi-R	**Vancomicina**, **Teicoplanina**, Linezolid, Daptomicina, Tigeciclina
VRE	**Linezolid**, Daptomicina, Tigeciclina

Sintesi e algoritmo terapeutico nei VRE



Arias CA, Contreras GA, Murray BE et al. Management of multidrug-resistant enterococcal infections. Clin Microbiol Infect 2010; 16(6):555-562

1: se BL, ampi/sulbactam 12-24 g/die; 2) genta o strepto; 3) 8-12 mg/kg/die; 4) includono: tige, doxi con rifa o fluorochinoloni (se suscettibili per singolo agente); 5) fino a 30 g/die; 6) quinupristin/dalfopristin sono raccomandati da AHA, Linezolid è stato usato per meningiti; 7) se imipenem MIC <32 mg/L. NOTA: MIC SECONDO CLSI

GRAM NEGATIVI

Table 1. Selected β-lactamases of gram-negative bacteria

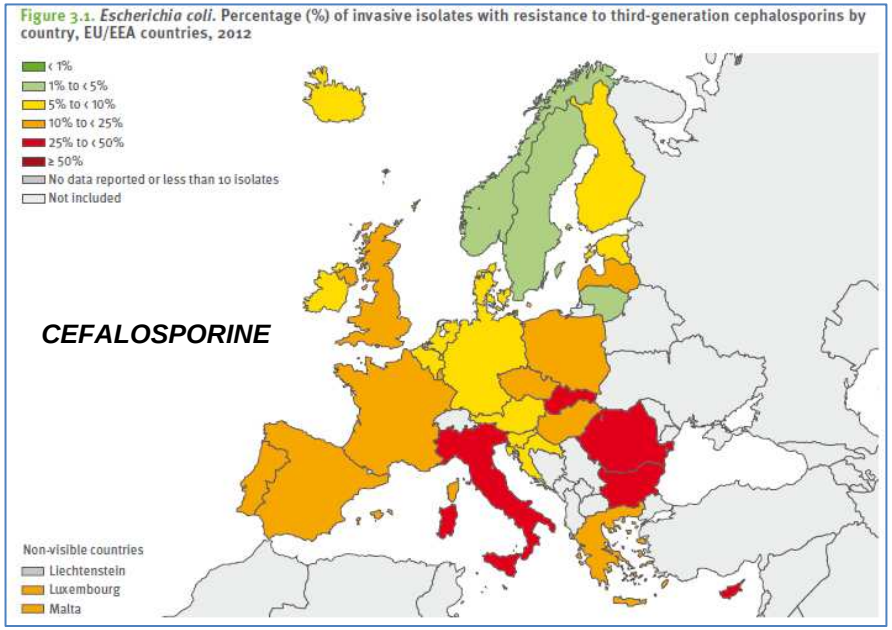
β-Lactamase	Examples	Substrates	Inhibition by clavulanate*	Molecular class
Broad-spectrum	TEM-1, TEM-2, SHV-1	Penicillin G, aminopenicillins, carboxypenicillins, piperacillin, narrow-spectrum cephalosporins	+++	A
	OXA family	Substrates of the broad-spectrum group plus cloxacillin, methicillin, and oxacillin	+	D
Extended-spectrum	TEM family, SHV family	Substrates of the broad-spectrum group plus oxyimino-cephalosporins, and monobactam (aztreonam)	++++	A
ESBL	CTX-M family	Substrates of the expanded-spectrum group plus, for some enzymes, cefepime	++++	A
	OXA family	Same as for CTX-M family	+	D
	Others (PER-1, PER-2, BES-1, GES/IBC family, SFO-1, TLA-1, VEB-1, VEB-2)	Same as for TEM family and SHV family	++++	A
AmpC	ACC-1, ACT-1, CFE-1, CMY family, DHA-2, FOX family, LAT family, MIR-1, MOX-1, MOX-2	Substrates of expanded-spectrum group plus cephamycins	0	C
Carbapenemase	IMP family, VIM family, GIM-1, SPM-1 (metallo-β-enzymes)	Substrates of the expanded-spectrum group plus cephamycins and carbapenems	0	B
KPC	KPC-1, KPC-2, KPC-3	Same as for IMP family, VIM family, GIM-1, and SPM-1	+++	A
PAN R	OXA-23, OXA-24, OXA-25, OXA-26, OXA-27, OXA-40, OXA-48	Same as for IMP family, VIM family, GIM-1, and SPM-1	+	D

Adapted from N Engl J Mea.[10]

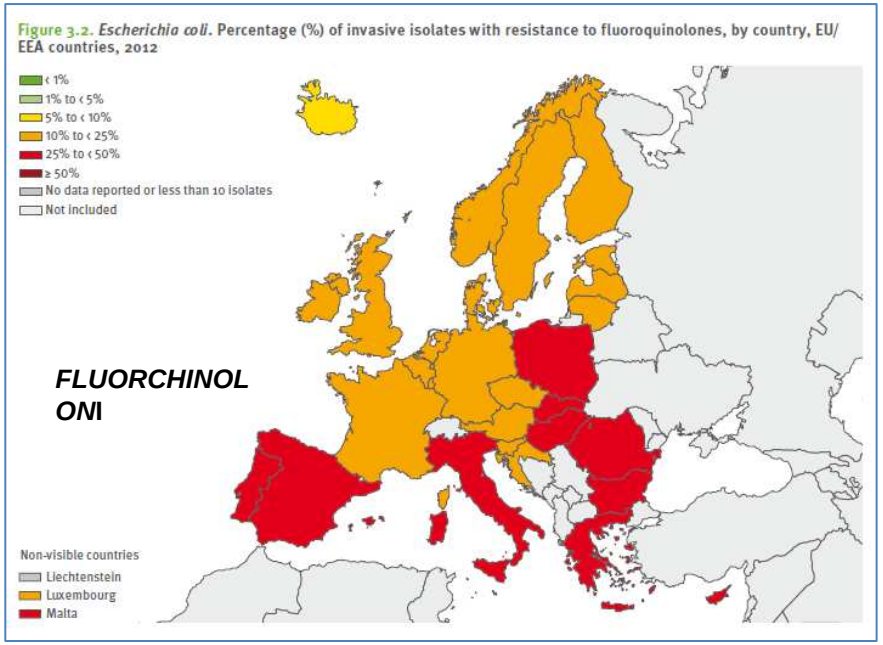
*+, +++, and ++++ denote relative sensitivity to inhibition.

ENTEROBATTERI
ESBL +

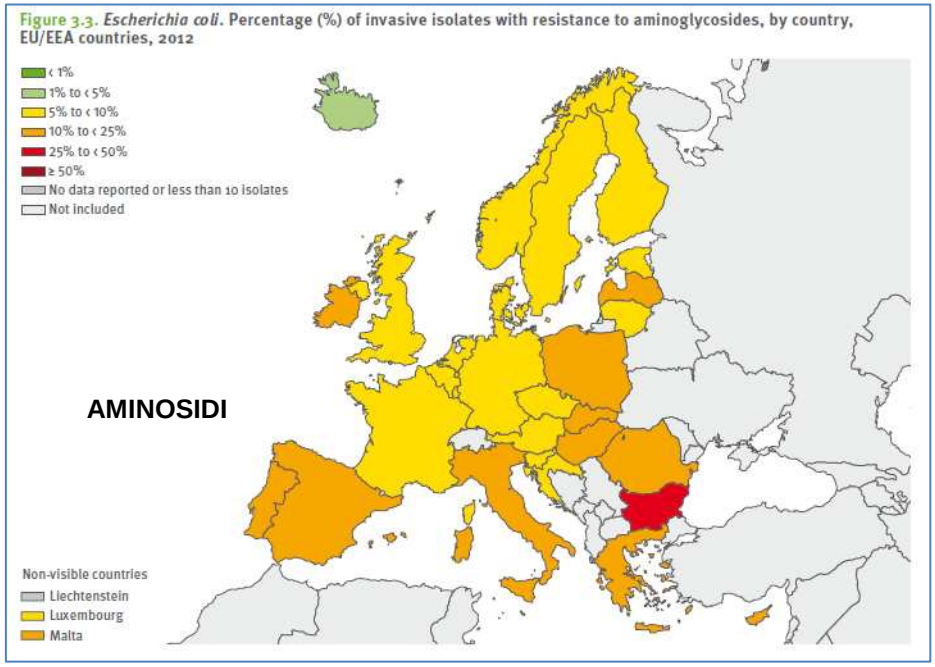
ESCHERICHIA COLI



CEFALOSPORINE



FLUORCHINOLONI



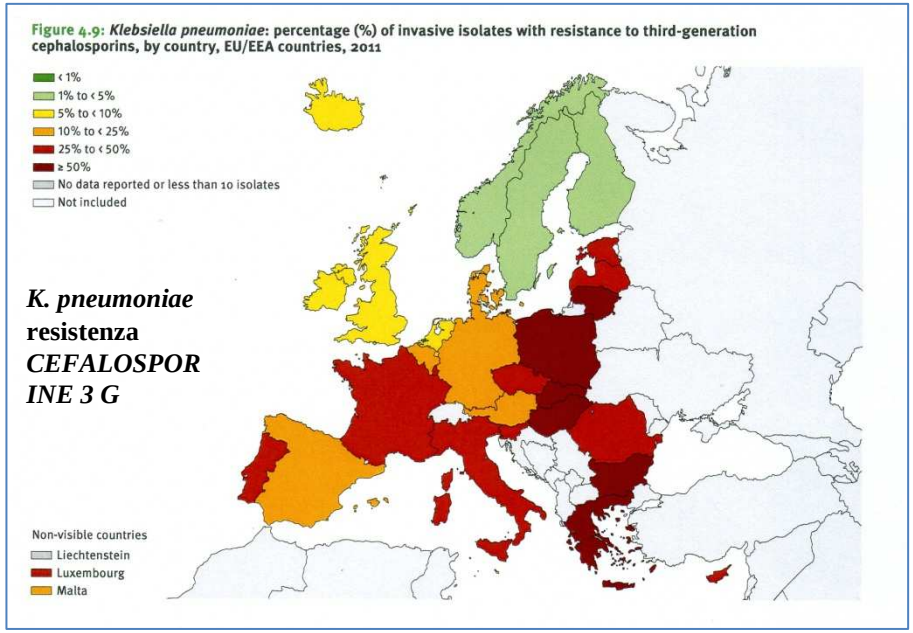
AMINOSIDI

ecdc 2012

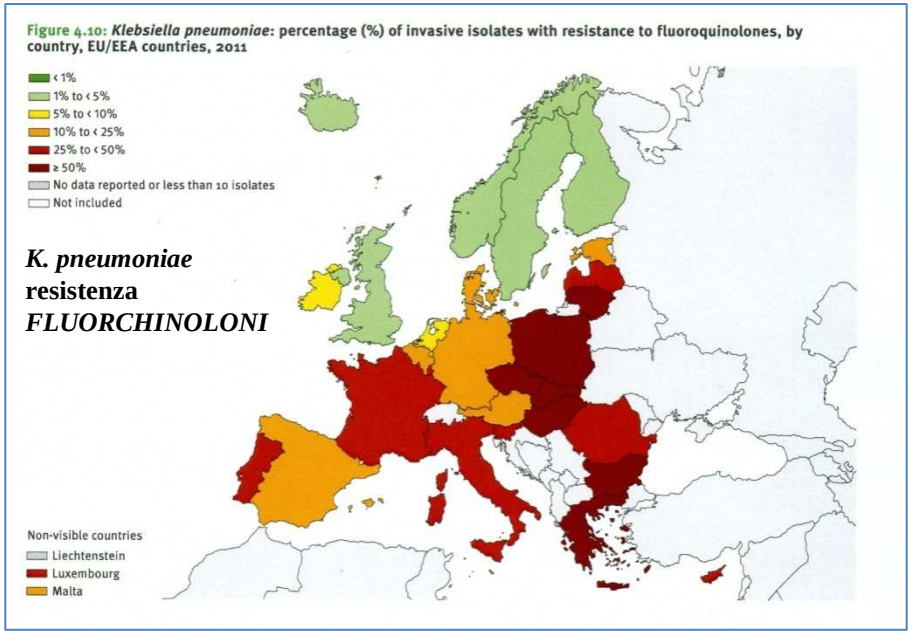
ESCHERICHIA COLI

KLEBSIELLA PNEUMONIAE

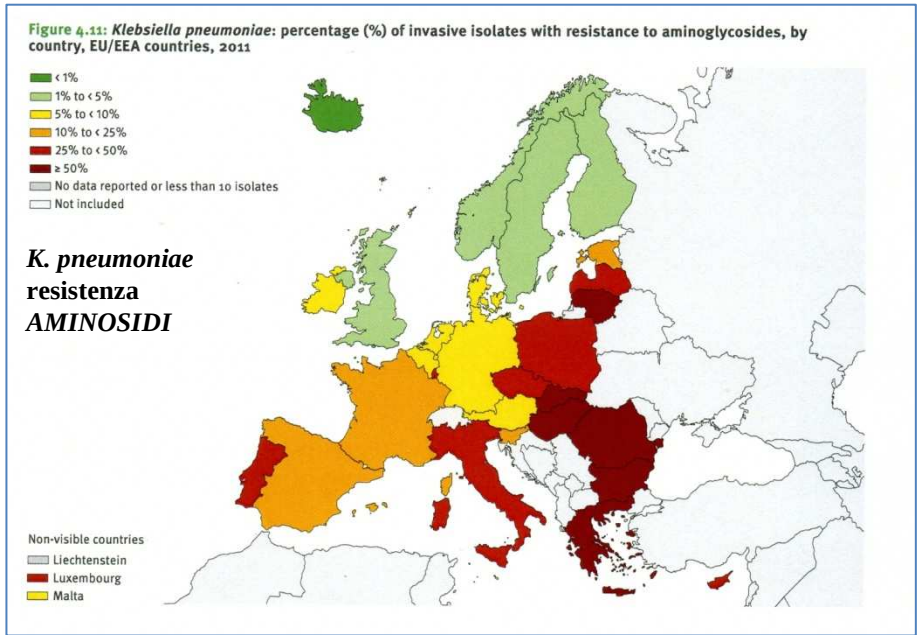
KLEBSIELLA PNEUMONIAE



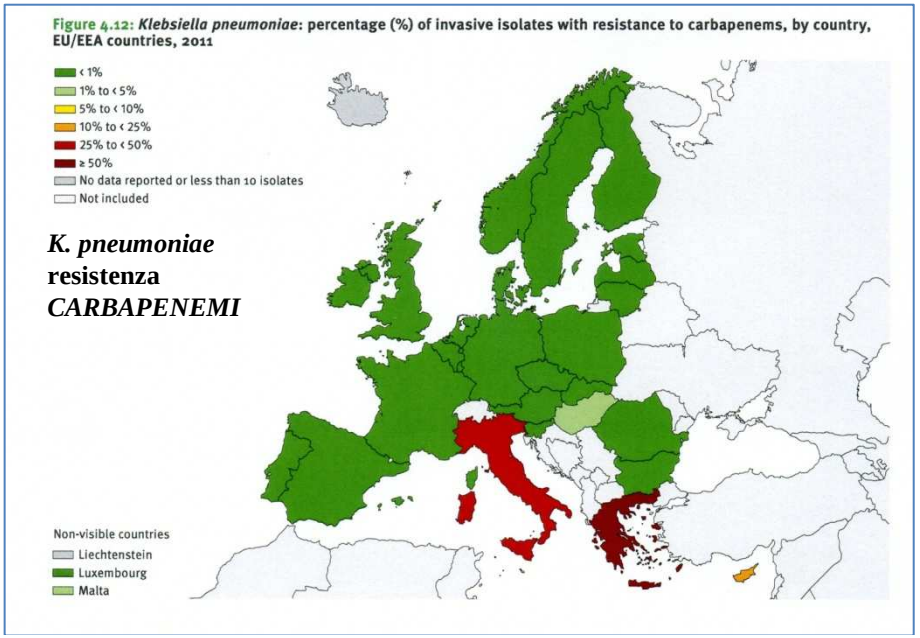
K. pneumoniae
resistenza
CEFALOSPORINE 3 G



K. pneumoniae
resistenza
FLUORCHINOLONI

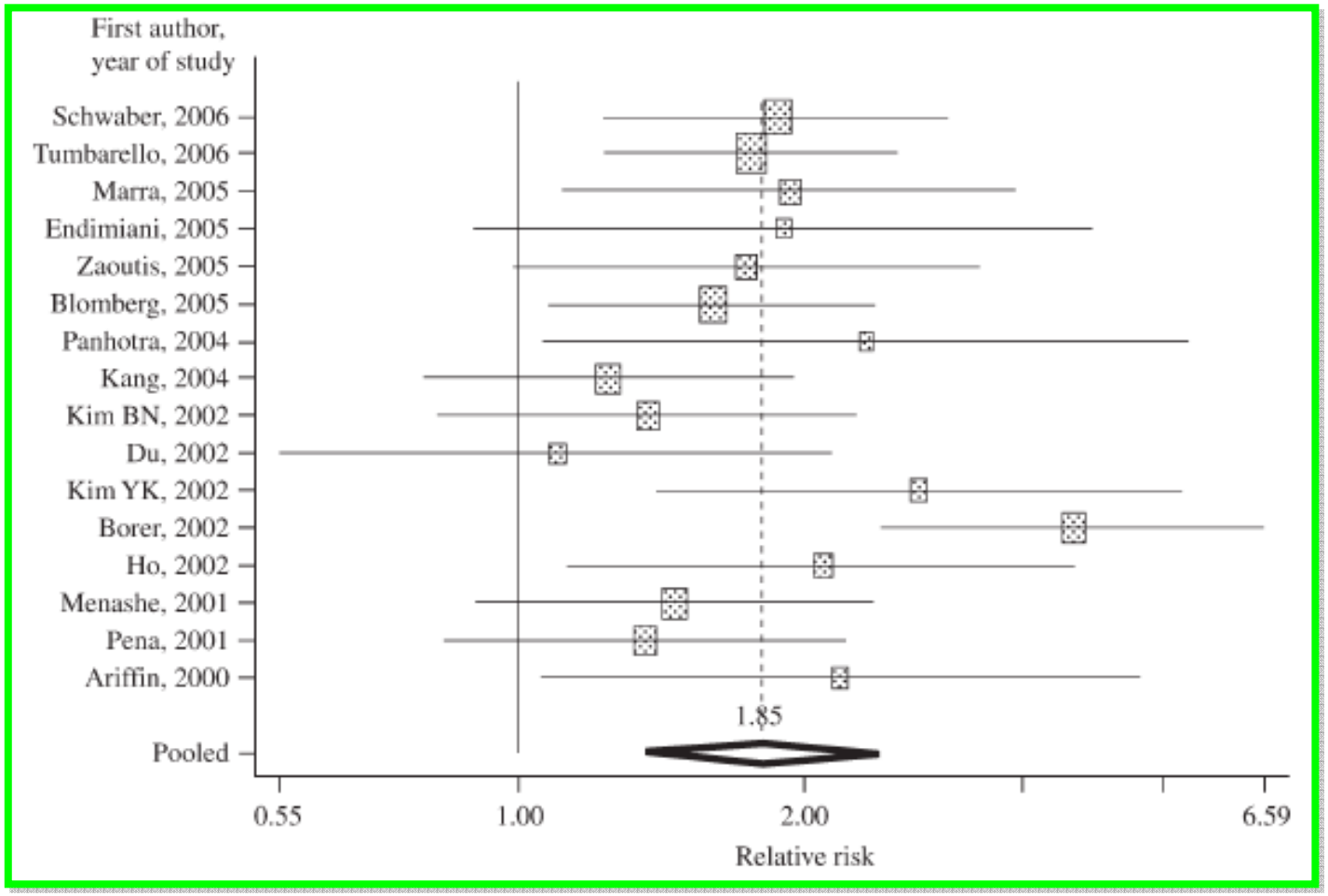


K. pneumoniae
resistenza
AMINOSIDI



K. pneumoniae
resistenza
CARBAPENEMI

Mortality in ESBL-producing vs. non-ESBL-producing *Enterobacteriaceae* bacteremia



Schwaber & Carmeli – JAC 2007

TERAPIA DELLE INFEZIONI DA ENTEROBATTERI PRODUTTORI DI ESBL

1. **IMIPENEM**
   MEROPENEM
   ERTAPENEM

2. **TIGECICLINA (non attiva su Proteus mirabilis e Proteus indolo+)**

3. **COLIMICINA (non attiva su Proteus spp., Providencia spp., Morganella morganii, Serratia marcescens)**

4. **FOSFOMICINA**

Disponible en ligne sur
SciVerse ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Médecine et maladies infectieuses

Médecine et maladies infectieuses 43 (2013) 62–66

Original article

Alternatives to carbapenems in ESBL-producing *Escherichia coli* infections

Alternatives aux carbapénèmes dans les infections à Escherichia coli producteurs de BLSE

D. Fournier [a], C. Chirouze [b], J. Leroy [b], P. Cholley [c,d], D. Talon [c,d], P. Plésiat [a], X. Bertrand [c,*,d]

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Available online 19 February 2013

Abstract

Objectives. – The authors had for objective to assess the activity of a wide panel of antibiotics on extended-spectrum-β-lactamase producing *Escherichia coli* isolates (ESBL-Ec), because of the sharp increase of their frequency, leading to an increased use of carbapenems.

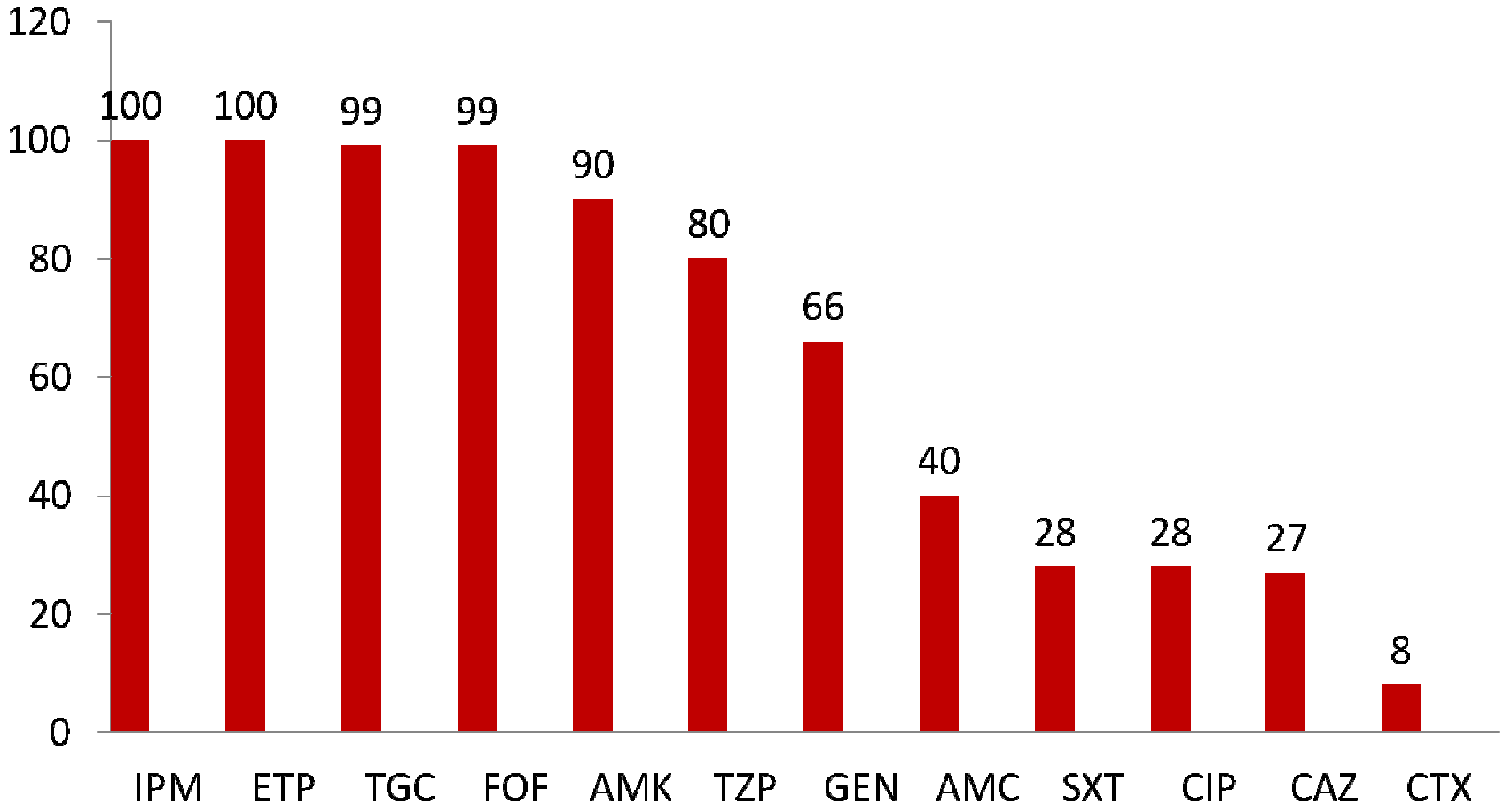
Material and methods. – We selected 100 ESBL-Ec in which ESBLs were identified by PCR and sequencing, between 2009 and 2010. We determined the MICs of amoxicillin-clavulanate, piperacillin-tazobactam, temocillin, mecillinam, cefoxitin, cefotaxime, ceftazidime, aztreonam, tigecycline, nitrofurantoin, and fosfomycin using reference methods. The susceptibility profiles were defined according to EUCAST 2012 recommendations.

Results. – Fosfomycin, nitrofurantoin, and pivmecillinam were active against more than 90% of isolates and remain excellent choices for the oral treatment of urinary tract infections (UTIs). Temocillin and piperacillin-tazobactam are also good candidates for the treatment of pyelonephritis or bloodstream infections. Only 27, 23, and 8% of isolates were susceptible to ceftazidime, cefepime, and cefotaxime, respectively.

Conclusion. – Our study results prove that in many cases, there are non-carbapenem alternatives for the treatment of ESBL-Ec infections.

Keywords: *Escherichia coli*; ESBL; Antibiotic resistance

Susceptibility (%) of extended-spectrum-β-lactamase (ESBL) producing Escherichia coli to various antibiotics



All Enterobacteriaceae species ($N = 152$)[a]		
Aztreonam	0(0)	0(0)
Cefepime	0(0)	0(0)
Cefotaxime	0(0)	0(0)
Ceftazidime	0(0)	0(0)
Ciprofloxacin	16(10.5)	0(0)
Colistin	111(73.0)	0(0)
Fosfomycin	141(92.8)	8(5.3)
Gentamicin	30(19.7)	16(10.5)
Imipenem	54(35.5)	42(27.6)
PIP/TAZ	0(0)	0(0)
Tetracycline	31(20.4)	33(21.7)
Tigecycline	140(92.1)	12(7.9)
SXT	19(12.5)	0(0)

LE NUOVE RESISTENZE

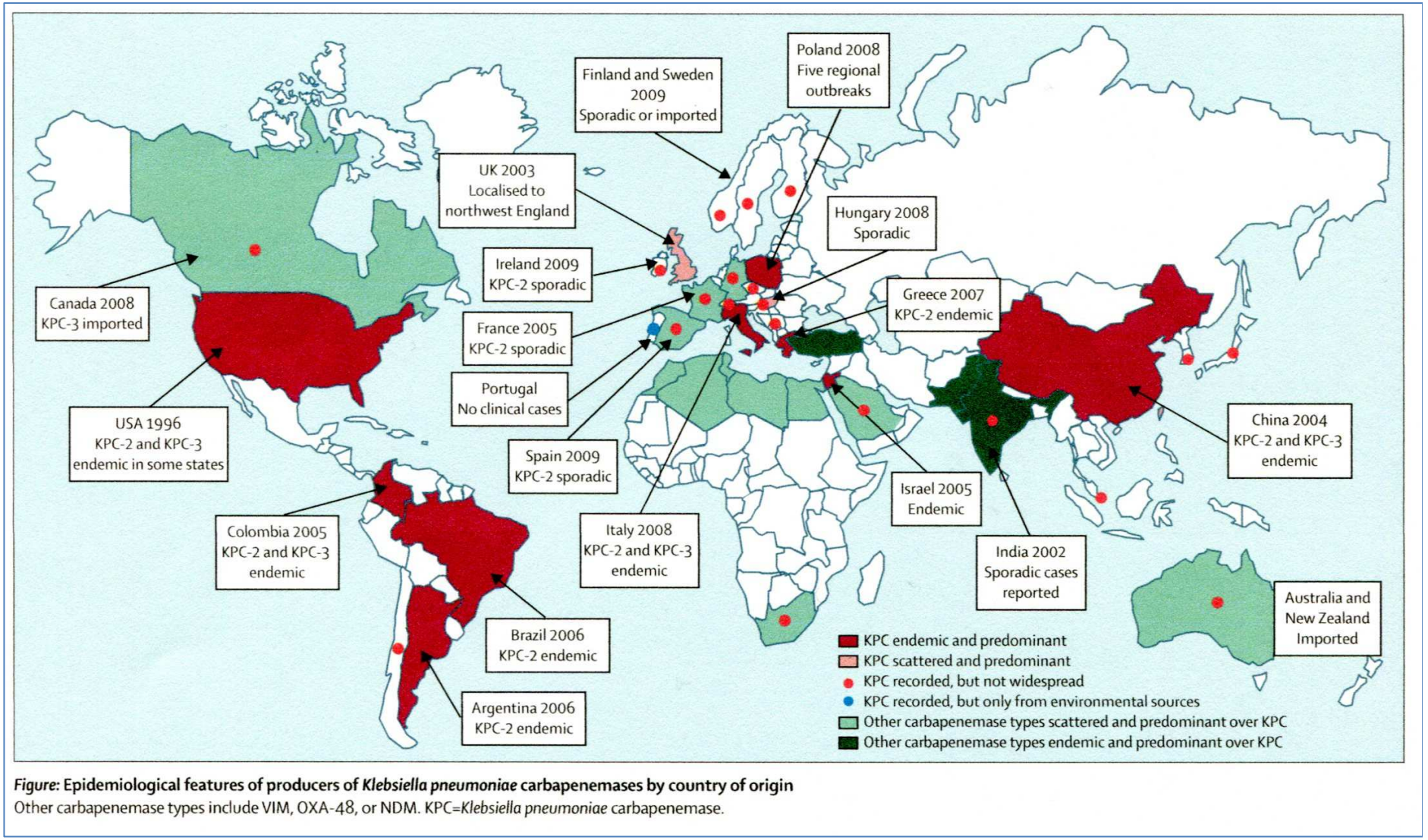
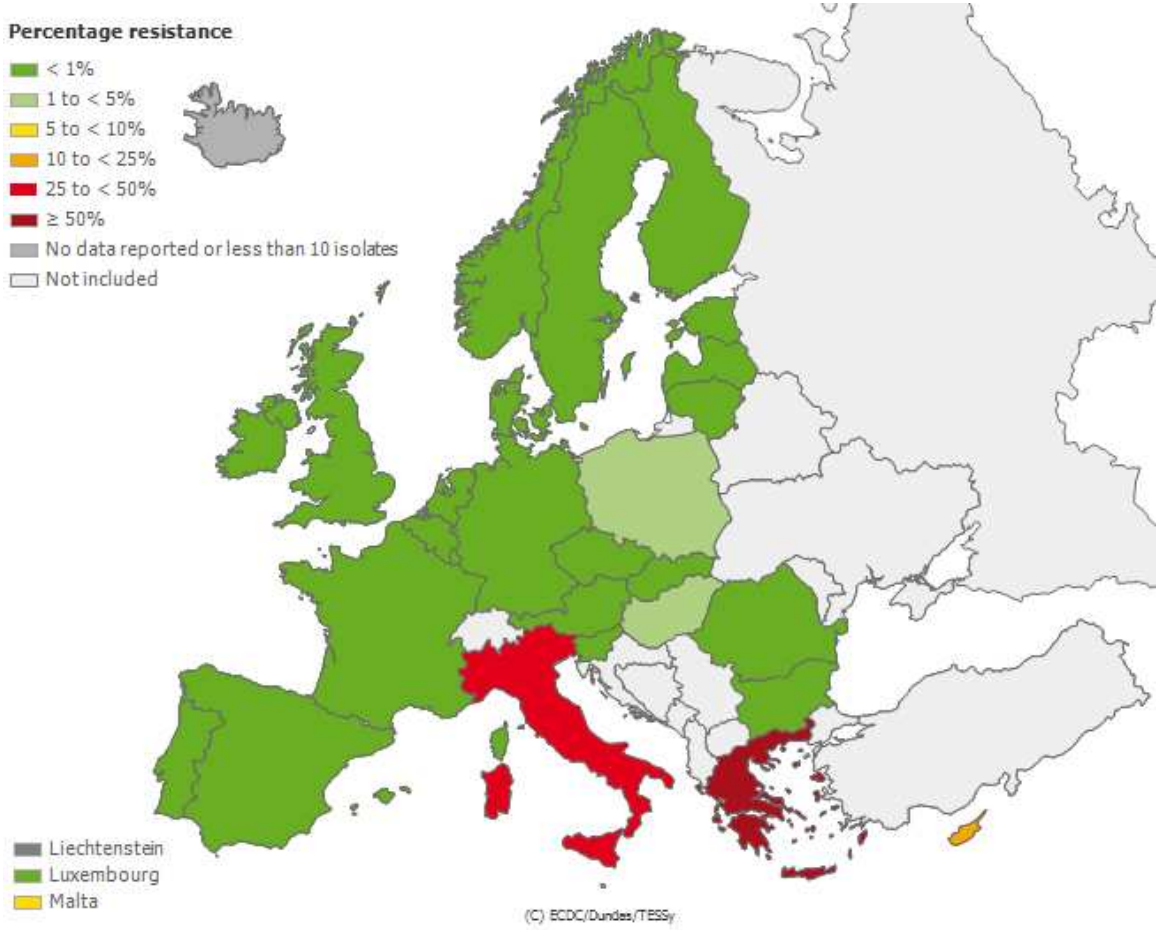


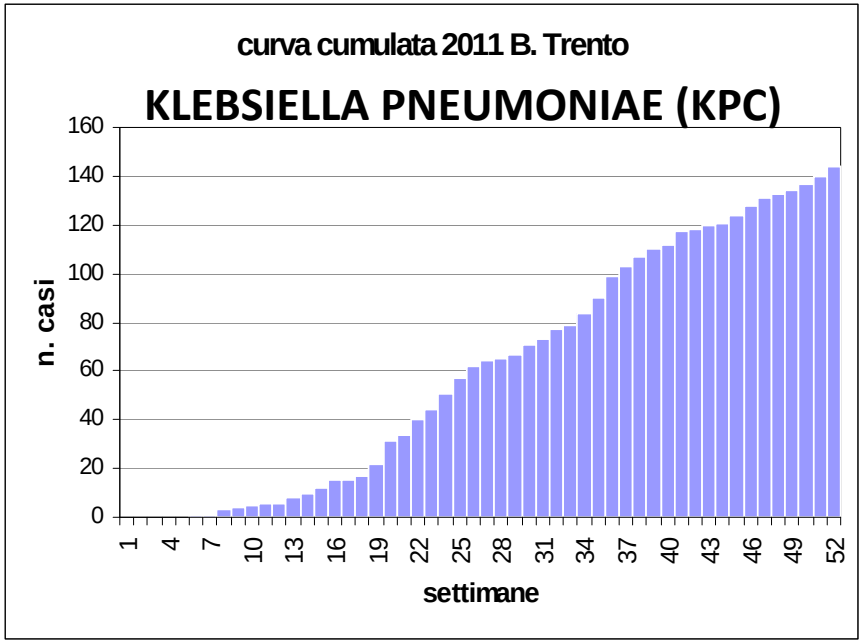
Figure: **Epidemiological features of producers of *Klebsiella pneumoniae* carbapenemases by country of origin**
Other carbapenemase types include VIM, OXA-48, or NDM. KPC=*Klebsiella pneumoniae* carbapenemase.

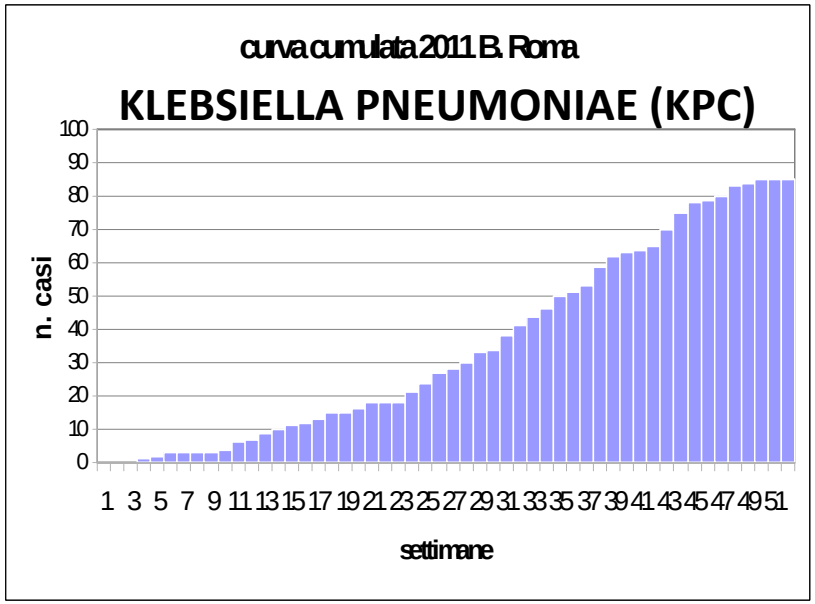
Lancet 2013

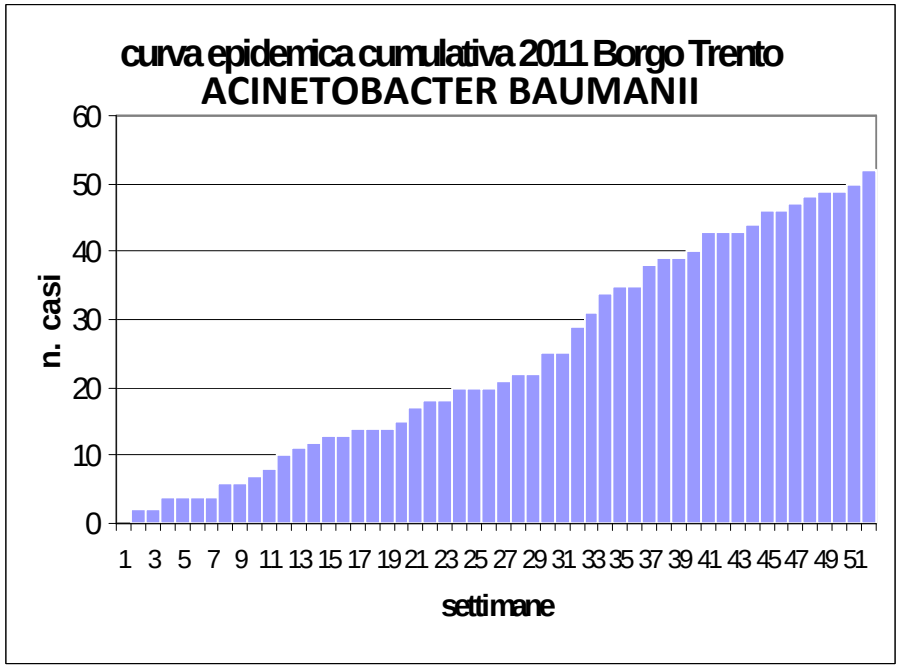
Proporzione di *K.pneumoniae* resistente ai carbapenemici (R +I) (2011)

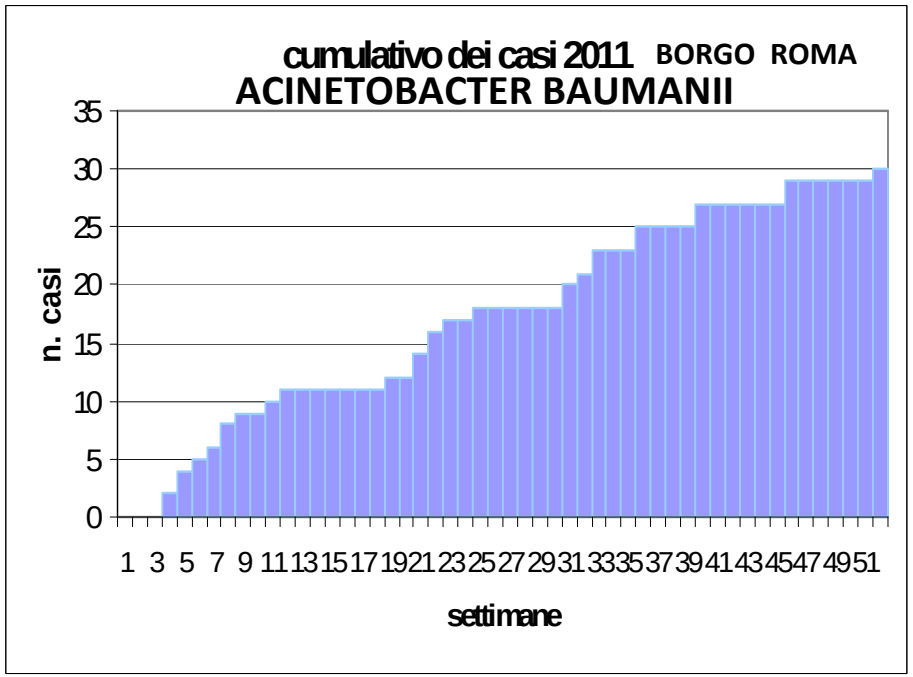


http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/maps_report.aspx (Aprile 2013)


curva cumulata 2011 B. Trento
KLEBSIELLA PNEUMONIAE (KPC)
n. casi
settimane

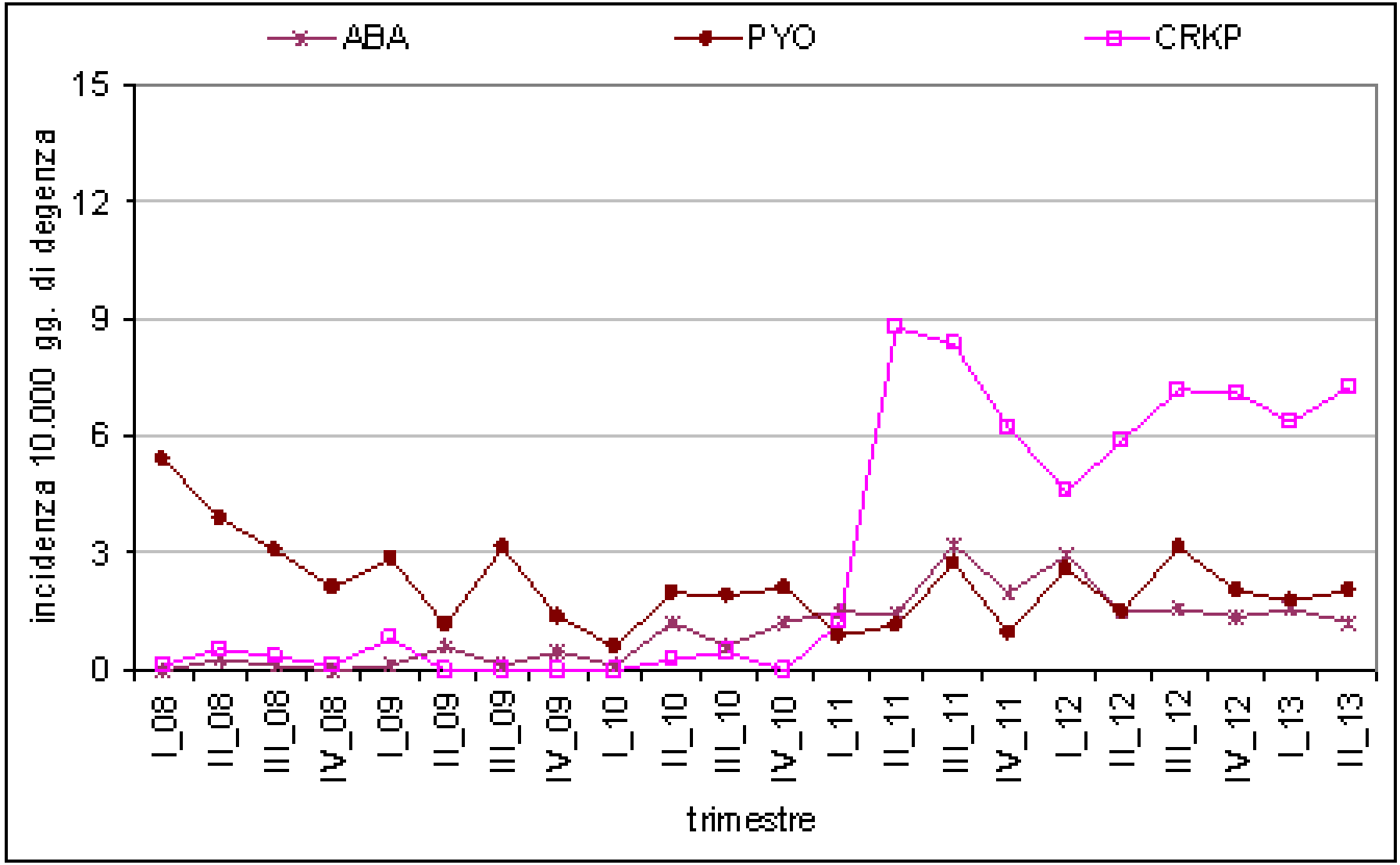

curva cumulata 2011 B. Roma
KLEBSIELLA PNEUMONIAE (KPC)
n. casi
settimane


curva epidemica cumulativa 2011 Borgo Trento
ACINETOBACTER BAUMANII
n. casi
settimane


cumulativo dei casi 2011 BORGO ROMA
ACINETOBACTER BAUMANII
n. casi
settimane

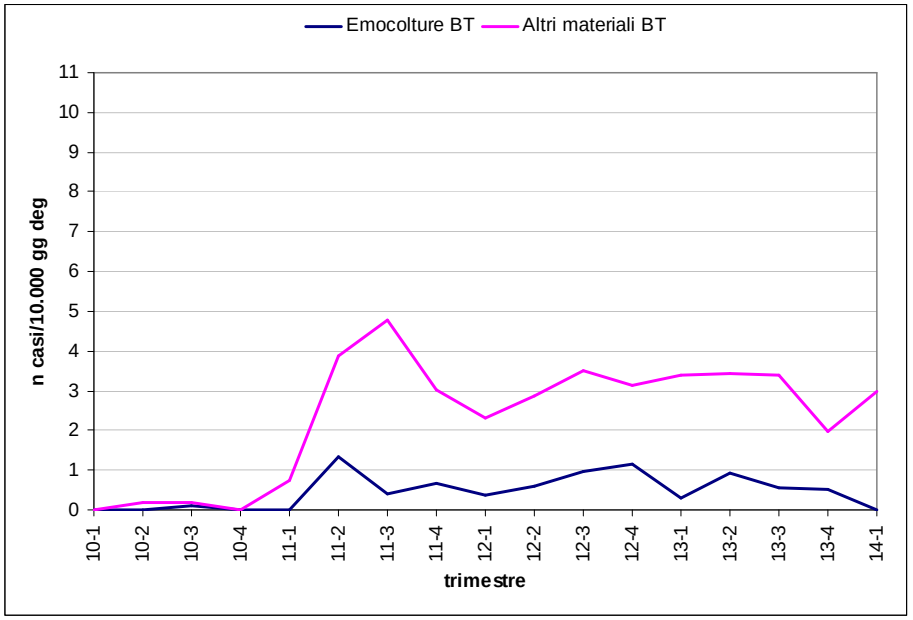
B. Trento

Acinetobacter baumani, Pseudomonas aeruginosa, Klebsiella pneumoniae

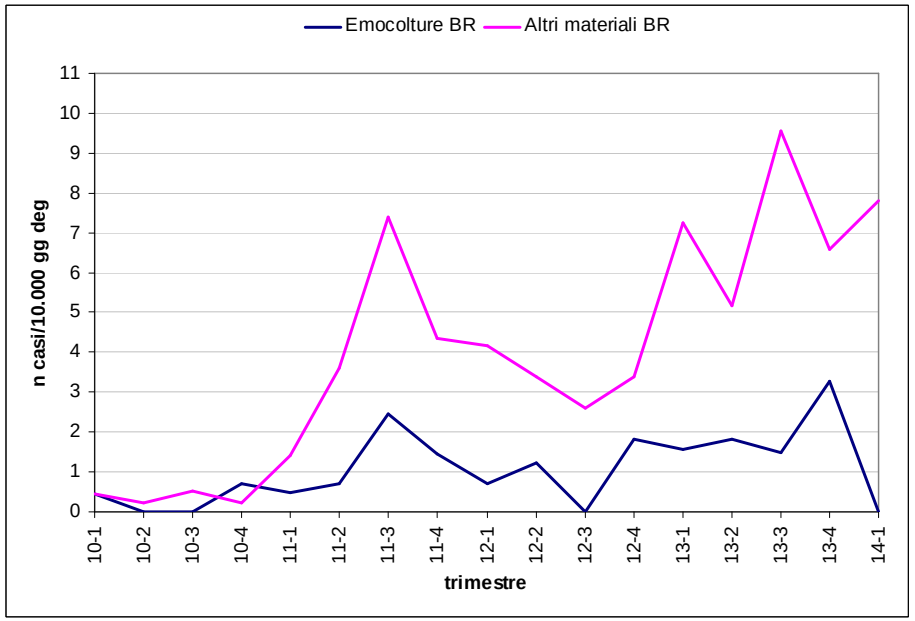


Incidenza di *K. pneumoniae* produttore di carbapenemasi presso i presidi ospedalieri dell'AUOI di Verona, 2010-2014*

Osp. Borgo Trento



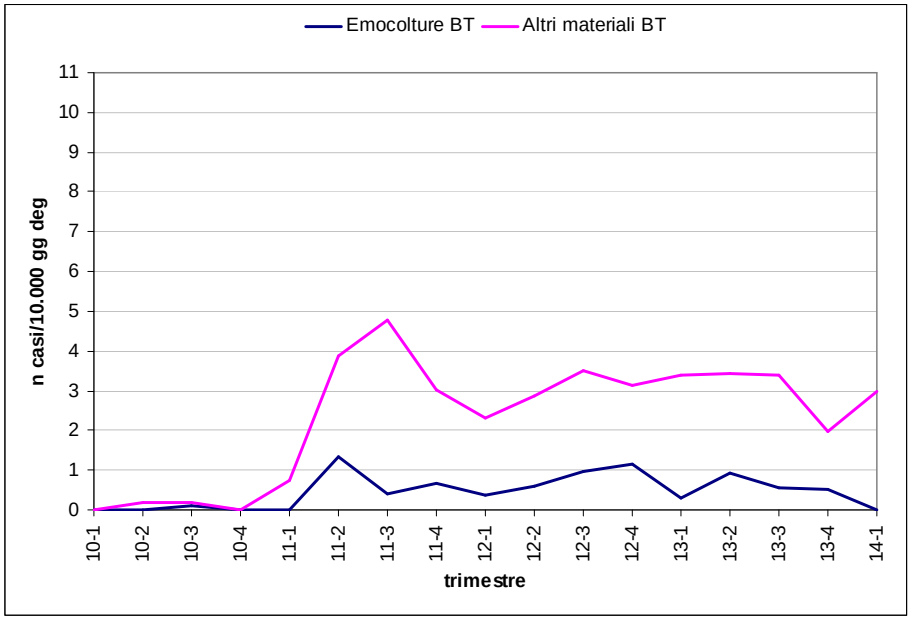
Osp. Borgo Roma



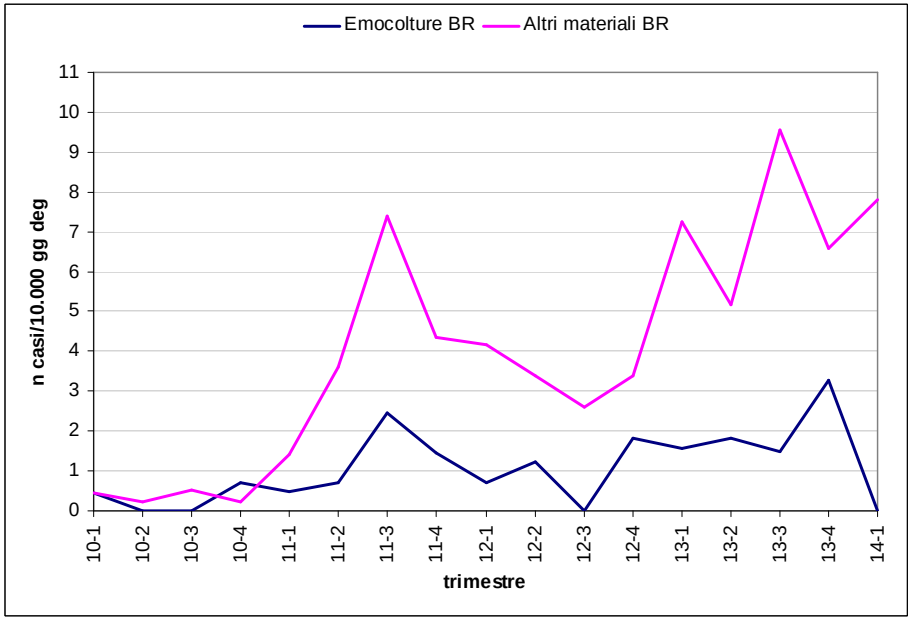
* fino al 28 febbraio 201

Incidenza di *K. pneumoniae* produttore di carbapenemasi presso i presidi ospedalieri dell'AUOI di Verona, 2010-2014*

Osp. Borgo Trento



Osp. Borgo Roma



* fino al 28 febbraio 201

Andamento dei casi di infezione / colonizzazione da K. pneumoniae produttore di carbapenemasi (CRKP) presso l'Azienda Ospedaliera Integrata di Verona

Caratteristiche dei pazienti con infezione/colonizzazione di *K. pneumoniae* produttore di carbapenemasi, alla 39ª settimana. Anno 2011.

	AOUI	B.go Trento	B.go Roma
Casi, N	174	111	63
Maschi, N(%)	81 (46.5)	45 (40.5)	36 (57.1)
Età			
media (range)	73.2 (21-97)	73.6 (21-97)	72.6 (22-93)
mediana (IQR)	78 (68-85)	78 (68.5-85)	77 (66-85)
Giorni dal ricovero			
media (range)	17.8 (0-79)	15.8 (0-68)	21.3 (1-79)
mediana (IQR)	13 (4-29)	12 (3.5-23.5)	17 (4-36)
Isolamento all'ingresso*, N(%)	37 (21.3)	25 (22.5)	12 (19.0)

* isolamento di CRKP entro 2 giorni dal ricovero

Protocolli di terapia delle infezioni da batteri multiresistenti

K. pneumoniae KPC: typical XDR phenotype

Antibiotic	MIC mg/L (S/I/R)
Amp/Sulb	>32 R
Pip/Tazo	>128 R
Ceftriaxone	>64 R
Ceftazidime	>64 R
Cefepime	>64 R
Ertapenem	>32 R
Imipenem	>32 R
Meropenem	>32 R
Aztreonam	>64 R
Amikacin	>64 R
Gentamicin	2 S
Tobramycin	>16 R
Ciprofloxacin	>4 R
Fosfomycin	32 S
Tigecycline	1.5 I
Colistin	0.4 S

Treatment options:

- Colistin
- Carbapenem (especially if MIC relatively low)
- Tigecycline (HD)
- Gentamicin
- Fosfomycin HD
- Rifampin (test synergy)

Combination regimens (open issues)

Hirsch & Tam – JAC 2010
Qureshi *et al* – AAC 2012
Tumbarello *et al* - CID 2012

Pazienti con isolamenti di batteri multiresistenti

1. Non trattare mai i pazienti colonizzati
2. Non usare mai la colimicina o la fosfomicina da sole
3. Nelle infezioni da germi multiresistenti la scelta dell'antibiotico e anche le dosi devono essere basate sul valore delle CMI in rapporto al breakpoint.
4. In caso di panresistenze occorre chiedere al laboratorio studi di sinergia in vitro
5. I tentativi di decolonizzare con antibiotici per via orale (gentamicina 80 mg x 3 /die) non hanno, a tutt'oggi, sufficiente ed adeguata documentazione

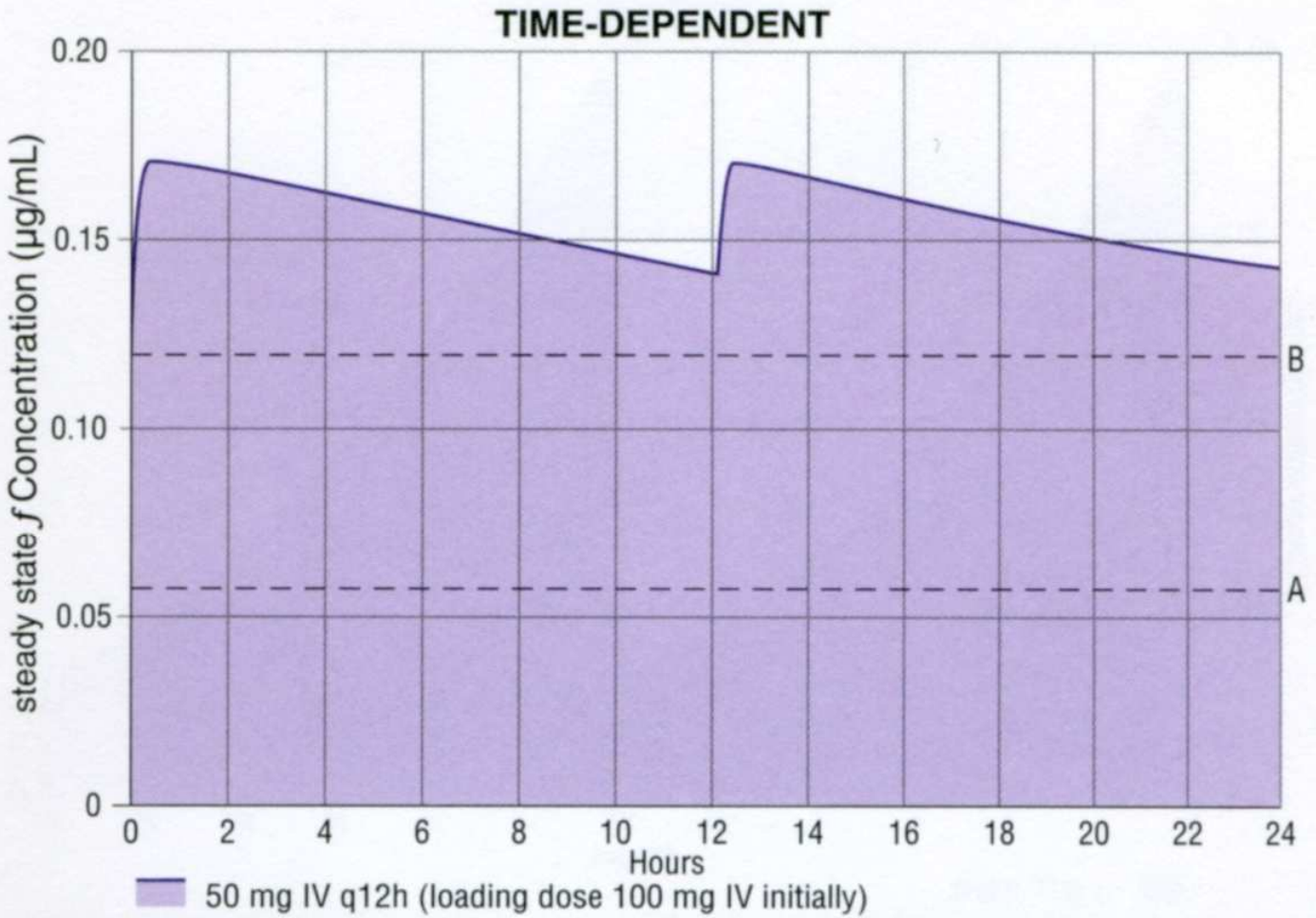
Terapia delle KPC (Kebsiella pneumoniae produttrice di carbapenemasi o altri enterobatteri produttori di carbapenemasi= CRE)

•COLIMICINA dose da carico 9 milioni poi
4,5 milioni x 2 /die
+
MEROPENEM* 1-2 gr x 3 /die
oppure
IMIPENEM* 1 gr x 3 /die

•COLIMICINA dose come sopra
+
MEROPENEM* dose come sopra
IMIPENEM* dose come sopra
+
FOSFOMICINA 4 gr x 4/die
Oppure
TIGECICLINA 100 o 150 mg x 2 / die

* Scelta basata sul valore della CMI ; il carbapenemico deve essere utilizzato anche nei casi in cui le CMI superino, non di molto, il breakpoint di resistenza

Tigecycline IV



	MIC_{90}	Pathogen
A	0.06	*Streptococcus pyogenes*
B	0.12	*Staphylococcus aureus* MSSA
	0.25	*Staphylococcus aureus* MRSA

HD Tigecycline?

TABLE 1. Tigecycline: dose-related serum and urinary concentrations

Tigecycline initial i.v. dose (mg)	Serum concn[d] (μg/ml)	Urinary concn[d] (μg/ml)
100[a]	~1.5	~0.3
200[b]	~3.0	~0.6
400[c]	~6.0	~1.2

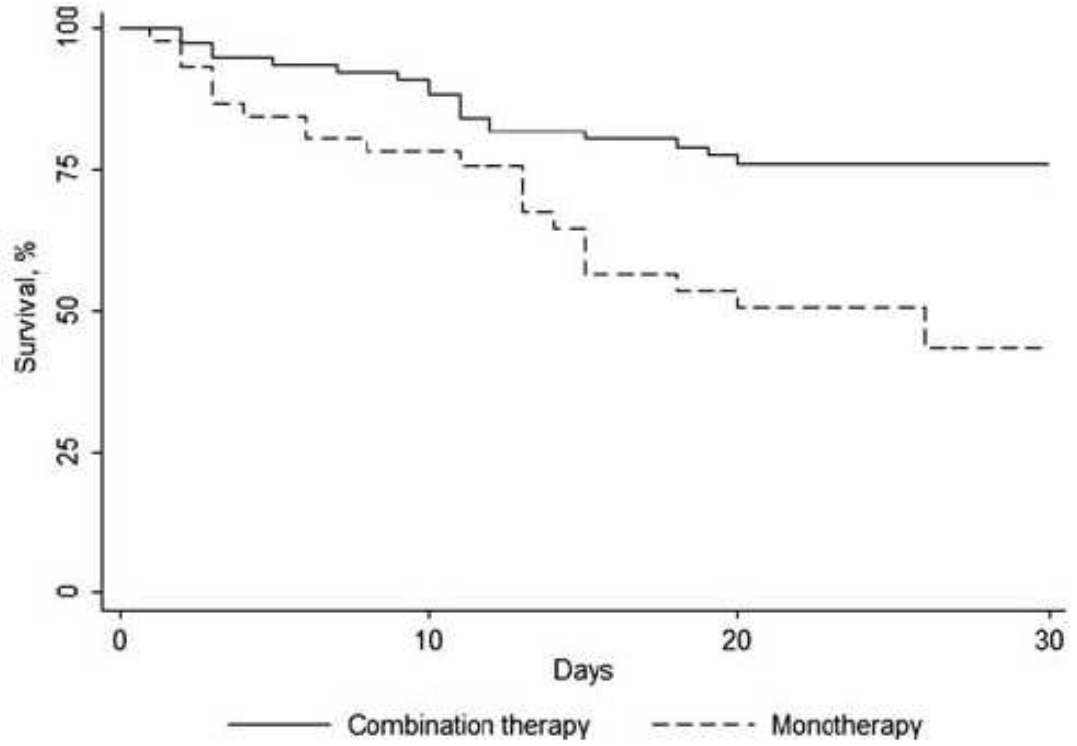
[a] Maintenance dose, 50 mg (i.v.) q12h.
[b] Maintenance dose, 100 mg (i.v.) q24h.
[c] Maintenance dose, 200 mg (i.v.) q24h.
[d] Values represent estimates.

B.A. Cunha JOURNAL OF CLINICAL MICROBIOLOGY, May 2009, p. 1613

Colimicina in corso di insufficienza renale

1. CrCl 20-50 : 75 % della dose ogni 12-24 ore
2. CrCl 10-20 : 50% della dose ogni 24 ore
3. C rCl <10 : 25 % della dose ogni 36 ore

MONOTERAPIA O ASSOCIAZIONI



Combination

Monotherapy

Figure 2. Kaplan-Meier curves showing the impact of combination therapy (solid line) versus monotherapy (dotted line) on 30-day mortality of patients with *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae* isolate bloodstream infections ($P = .002$).

Tumbarello M et al. CID 2012;55:943-50

Efficacy of antimicrobial regimens used to treat infections caused by carbapenemase-producing *Klebsiella pneumoniae*

Antibiotic regimen	No. of patients (%)	Outcome success (%)	Failure (%)
MONOTHERAPY			
Colistin	64 (24.2)	35 (54.7)	29 (45.3)
Tigecycline	8 (4.7)	5 (62.5)	3 (37.5)
Aminoglycoside	16 (6.8)	12 (75.0)	4 (25.0)
Carbapenem	23 (9.8)	18 (78.3)	5 (21.7)
Total	111 (47.5)	70 (63.1)	41 (36.9)
COMBINATION THERAPY			
Two or more active drugs (carbapenem not included)	52 (22.2)	38 (73.1)	14 (26.9)
Two or more active drugs (carbapenem included)	30 (12.8)	28 (93.3)	2 (6.7)
Total	82 (35.0)	66 (88.5)	16 (19.5)
“Inappropriate” therapy	41 (17.5)	23 (56.1)	18 (43.9)
Total	234 (100)	159 (67.9)	75 (32.1)

M. Akova 2012

Empiric antibiotic therapy in wards wth KPC-Kp epidemic

- Sepsis syndrome, site of infection defined or not
- Intestinal colonization UK
- Blood cultures, TA, BAL, urine, etc.
- Meropenem ev 2 g tid (100 ml SF in 4 hrs)
- Gentamicin ev 240 mg od (100 ml SF in 1 h)
- Tigecycline ev 100 mg bid (250 ml SF in 4 hrs)

Menichetti

Background: Infections caused by multidrug-resistant gram-negative bacteria have caused a resurgence of interest in colistin. To date, information about pharmacokinetics of colistin is very limited in critically ill patients, and no attempts have been made to evaluate its concentration in BAL.
Methods: In this prospective, open-label study, 13 adult patients with ventilator-associated pneumonia caused by gram-negative bacteria were treated with colistin methanesulfonate (CMS) IV, 2 million International Units (174 mg) q8h, a usually recommended dose, for at least 2 days. Blood samples were collected from each patient at time intervals after the end of infusion. BAL was performed at 2 h. Colistin was measured by a selective, sensitive high-performance liquid chromatography-based method. Pharmacokinetic parameters were determined by noncompartmental analysis.
Results: Patients received 2.19 ± 0.38 mg/kg (range, 1.58-3.16) of CMS per dose. At steady state, mean ± SD plasma colistin maximum (Cmax) and trough (Ctrough) concentrations were 2.21 ± 1.08 and 1.03 ± 0.69 μg/mL, respectively. Mean ± SD area under the plasma concentration-time curve from 0 to 8 h (AUC_{0-8}), apparent elimination half-life, and apparent volume of distribution were 11.5 ± 6.2 μg × h/mL, 5.9 ± 2.6 h, and 1.5 ± 1.1 L/kg, respectively. Cmax/minimum inhibitory concentration (MIC) ratio and AUC_{0-24}/MIC ratio (MIC = 2 μg/mL) were 1.1 ± 0.5 and 17.3 ± 9.3, respectively. Colistin was undetectable in BAL. Nephrotoxicity was not observed.
Conclusions: Although the pharmacodynamic parameters that better predict the efficacy of colistin are not known in humans, in critically ill adult patients the IV administration of CMS 2 million International Units (174 mg) q8h results in apparently suboptimal plasma concentrations of colistin, which is undetectable in BAL. A better understanding of the pharmacokinetic-pharmacodynamic relationship of colistin is urgently needed to determine the optimal dosing regimen.

CHEST 2010; 138(6):1333–1339

Abbreviations: AUC = area under the plasma concentration-time curve; CF = cystic fibrosis; CL/fm = apparent total body clearance of formed colistin; Cmax = maximum concentration; CMS = colistin methanesulfonate; Ctrough = minimum concentration at predose; HPLC = high-performance liquid chromatography; Kel = apparent elimination rate constant; MIC = minimum inhibitory concentration; $t_{1/2}$ = apparent elimination half-life; Vd/fm = apparent volume of distribution of formed colistin

Colimicina nel BAL

In caso di VAP o HAP

La colimicina deve essere somministrata anche per via aerosolica alla dosi di

1.000.000 per 3 /die

(esiste la possibilità di broncospasmo)

- COLISTIN BLADDER INSTILLATION:

3,5 mg dissolved in 500 ml of saline solution through a triple catheter x 7days

Infection 2014 R. Giua et al.

ACINETOBACTER

Table I: Prevalence and susceptibility trends of *Acinetobacter baumannii* at Detroit Medical Center, 2003-2008

Year	No of Isolates	No[1]/1,000 Pt.[2] Days	Imipenem	Amp[3]/Sulbactam	Ceftazidime	Ciprofloxacin	TMP/SMX[4]	Amikacin	Tobramycin
2003	566	1.7	99%	89%	36%	32%	33%	90%	41%
2004	593	1.7	97%	86%	43%	31%	31%	77%	36%
2005	890	2.8	99%	87%	28%	24%	26%	81%	28%
2006	751	2.3	99%	62%	26%	24%	27%	92%	56%
2007	1175	3.6	65%	37%	16%	14%	17%	63%	60%
2008	1239	3.7	42%	40%	15%	15%	18%	33%	65%

[1] No= Number; [2] Pt.=patient; [3] Amp=ampicillin; [4] TMP/SMX= trimethoprim/sulfamethoxazole

Reddy T et al. Antimicrob Agents Chemother 2010

Terapia delle infezioni da Acinetobacter multiresistente

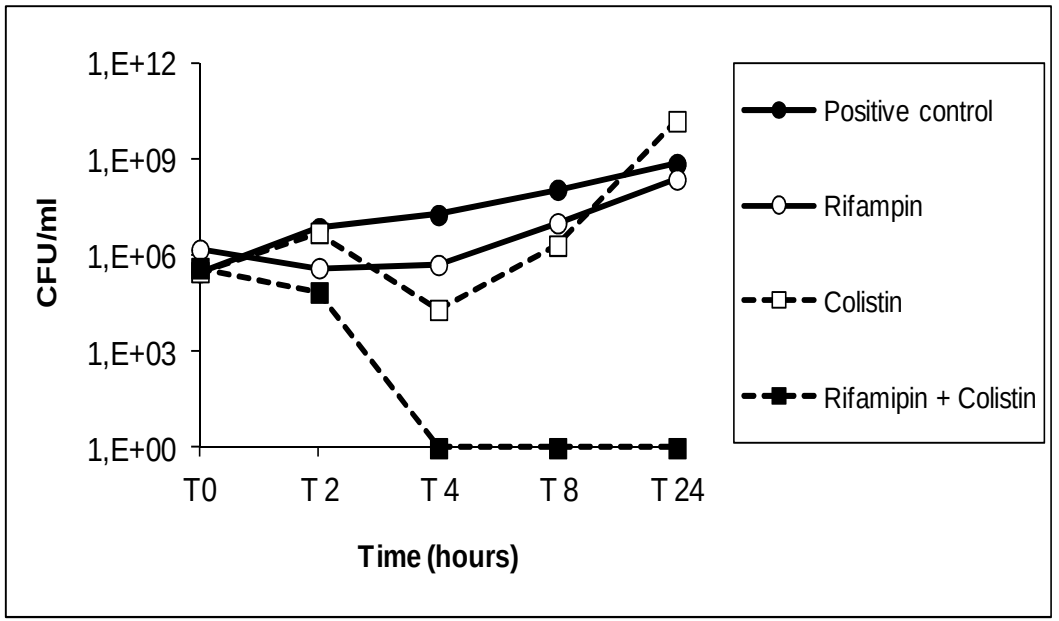
1. Ampicillina /Sulbactam 3 gr x 4 /die*
2. Colimicina 9 milioni dose da carico
   poi 4,5 milioni x 2
   +
   Rifampicina 600-900 mg / die
   +/-
   Imipenem o Meropenem**
   anche se resistenti ma con CMI relativamente basse
3. Colimicina dose come sopra
   +
   Tigeciclina 100 mg poi 50 mg x 2 ***
   (la dose può essere aumentata sino a 100/150 mg x 2 / die)
4. Colimicina (dose come sopra)
   +
   Ampicillina/Sulbactam 3 gr x 4 / die*

*** Alcuni autori consigliano 16 g di Ampicillina/sulbactam (3 gr x 6)**

**** La triplice terapia (colimicina + rifampicina + carbapenemico è consigliabile nel caso di un grave quadro settico).**

**** * L'associazione colimicina + tigeciclina non è consigliata nel caso di HAP o VAP**

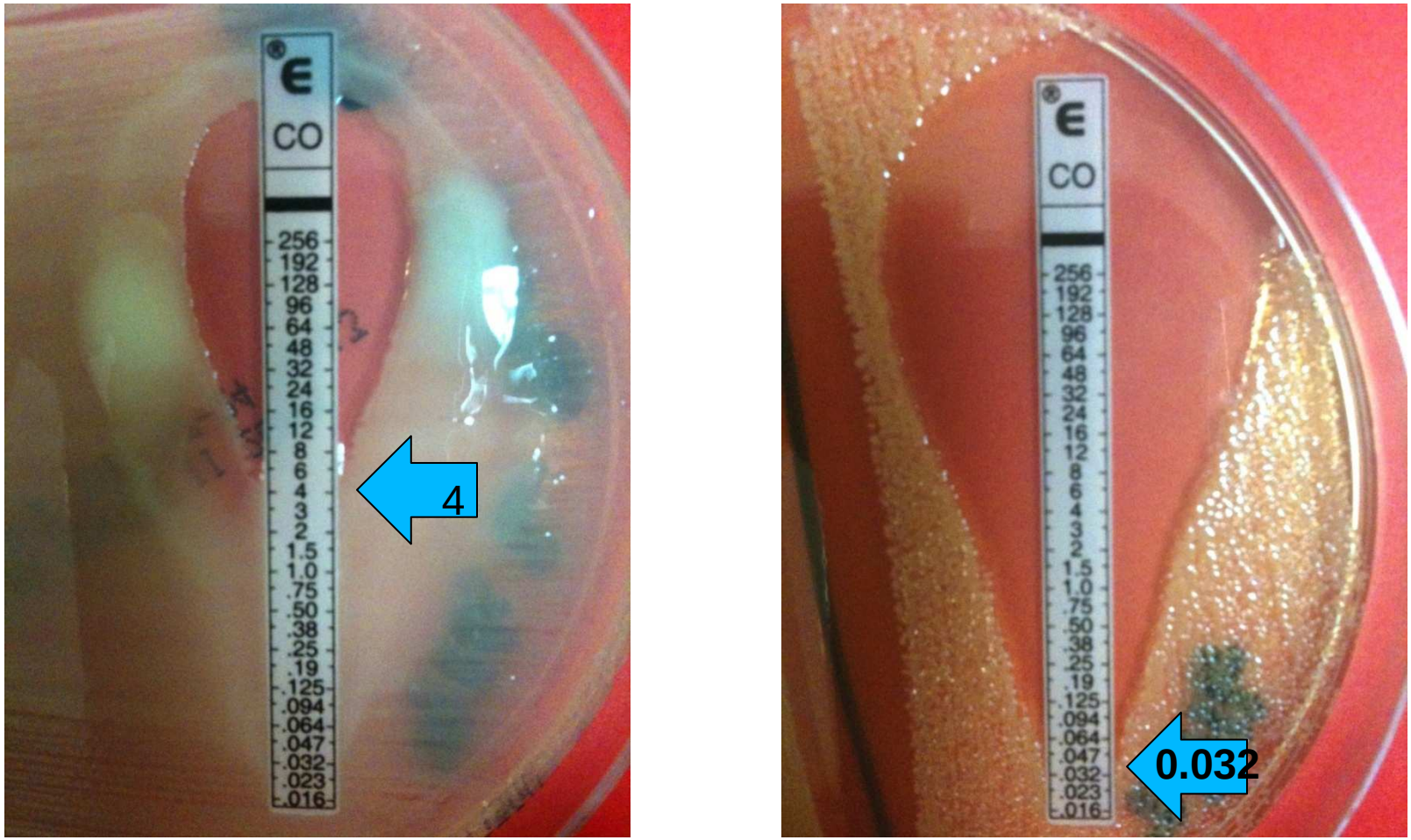
Rifampin plus Colistin time-kill curve vs. MDR *P. aeruginosa*



Tascini C. et al: Microbiological activity and clinical efficacy of a colistin and rifampin combination in multidrug-resistant *Pseudomonas aeruginosa* infections.
J Chemother. 2004 Jun;16(3):282-7.

F. Menichetti – Infection 2010

Colistin MIC vs KPC-Kp with Etest on MHB agar alone (left) and supplemented with Rifampin 32 mg/L (right)



Colistin susceptibility breakpoint 2 mg/L

Rifampin peak serum level 4-32 mg/L (600 mg po

Durante Mangoni et al. CID 2013

Colistin and Rifampicin Compared With Colistin Alone for the Treatment of Serious Infections Due to Extensively Drug-Resistant *Acinetobacter baumannii*: A Multicenter, Randomized Clinical Trial

Table 2.
Efficacy Outcomes

Outcome	Colistin + Rifampicin Arm (n = 104)	Colistin Arm (n = 105)	*P* Value
Primary outcome			
30-d mortality			
Yes	45 (43.3%)	45 (42.9%)	.95[a]
No	59 (56.7%)	60 (57.1%)	
Secondary outcomes			
Infection-related death at 30 d			
Yes	22 (21.15%)	28 (26.6%)	.29[a]
No	23 (22.1%)	17 (16.2%)	
Acinetobacter baumannii eradication			
Yes	63 (60.6%)	47 (44.8%)	.034[a]
No	38 (36.5%)	54 (51.4%)	
Median hospitalization length, d (IQR)	41 (26–61)	44 (27–59)	.96[b]
Development of colistin resistance, %	0	0	…

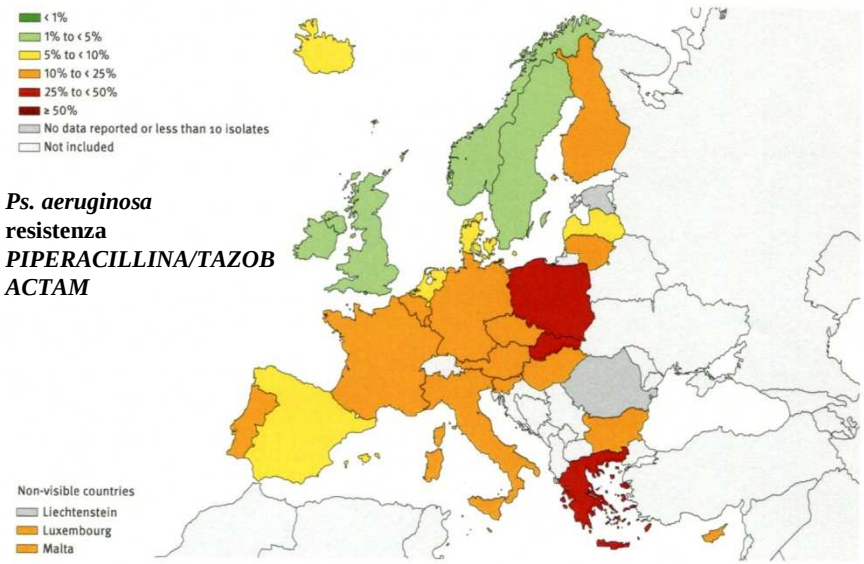
Data are reported as No. (%) unless otherwise specified.

Abbreviation: IQR, interquartile range.

PSEUDOMONAS AERUGINOSA

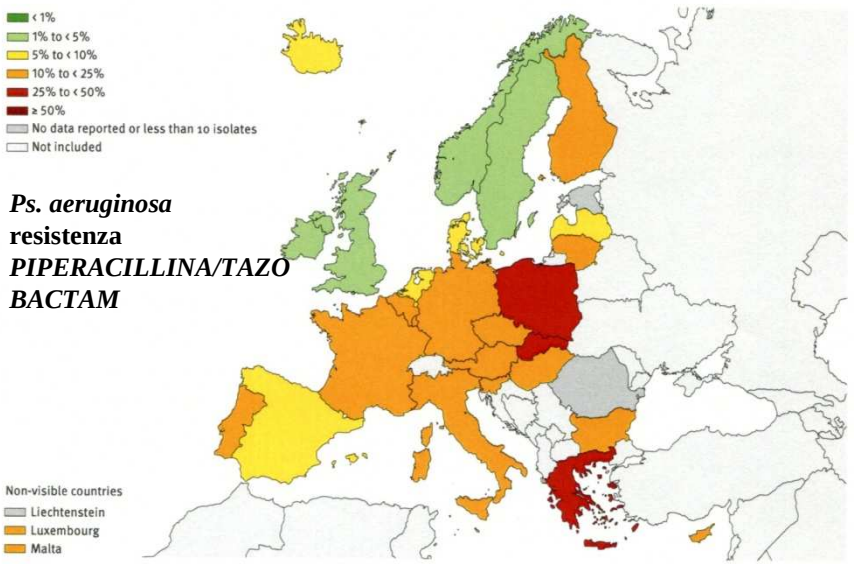
PSEUDOMONAS AERUGINOSA

Figure 4.19: *Pseudomonas aeruginosa*: percentage (%) of invasive isolates with resistance to piperacillin±tazobactam, by country, EU/EEA countries, 2011



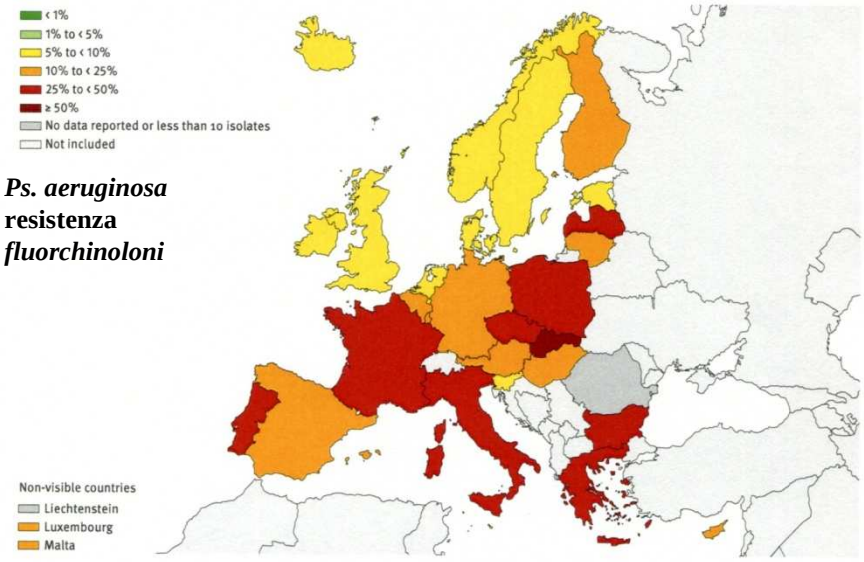
Ps. aeruginosa
resistenza
PIPERACILLINA/TAZOBACTAM

Figure 4.19: *Pseudomonas aeruginosa*: percentage (%) of invasive isolates with resistance to piperacillin±tazobactam, by country, EU/EEA countries, 2011



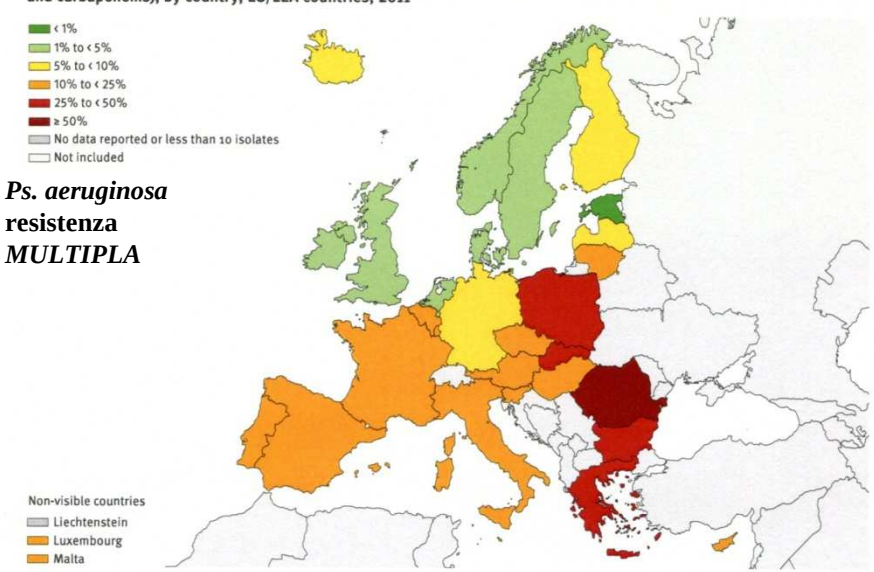
Ps. aeruginosa
resistenza
PIPERACILLINA/TAZOBACTAM

Figure 4.21: *Pseudomonas aeruginosa*: percentage (%) of invasive isolates with resistance to fluoroquinolones, by country, EU/EEA countries, 2011



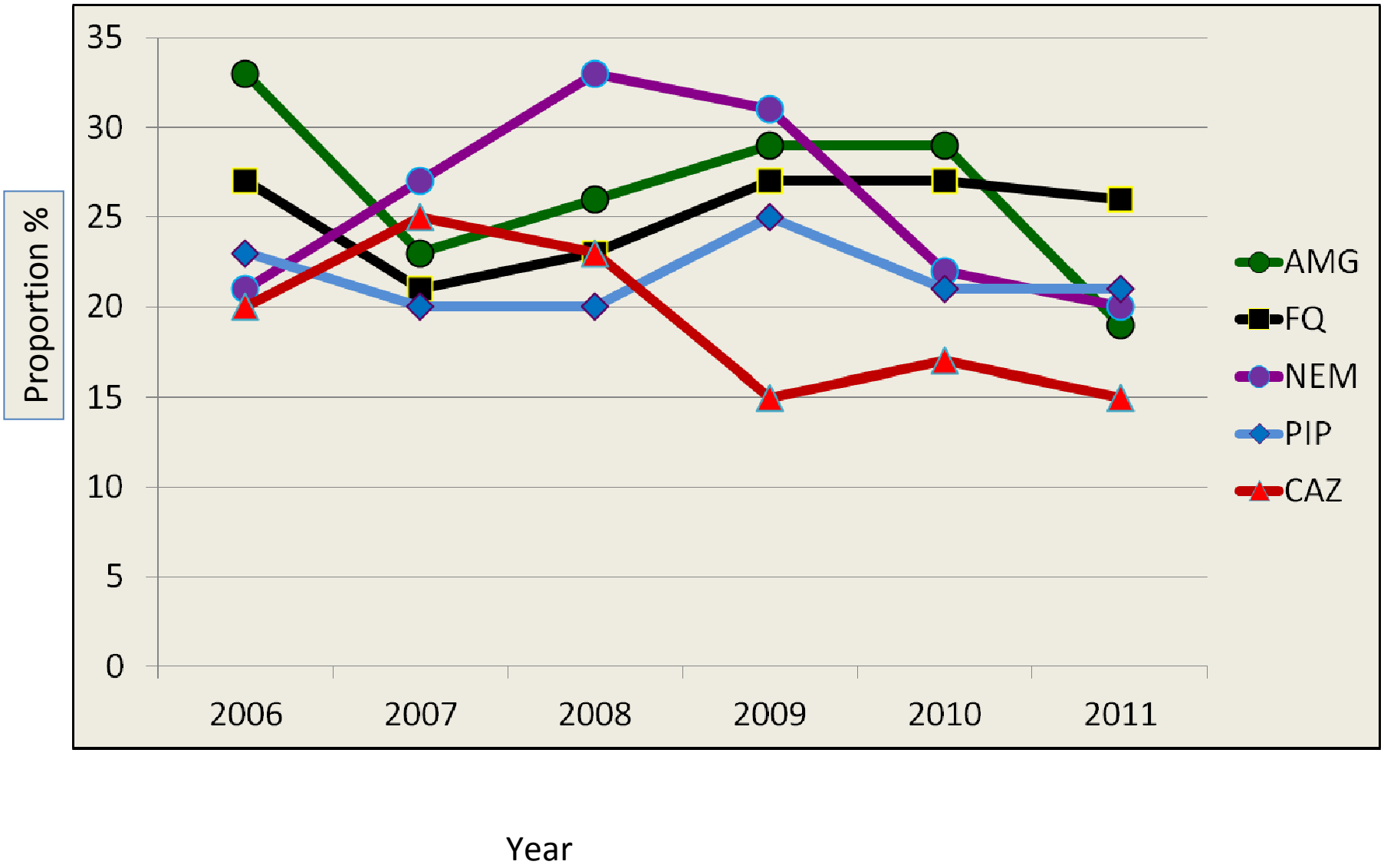
Ps. aeruginosa
resistenza
fluorchinoloni

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

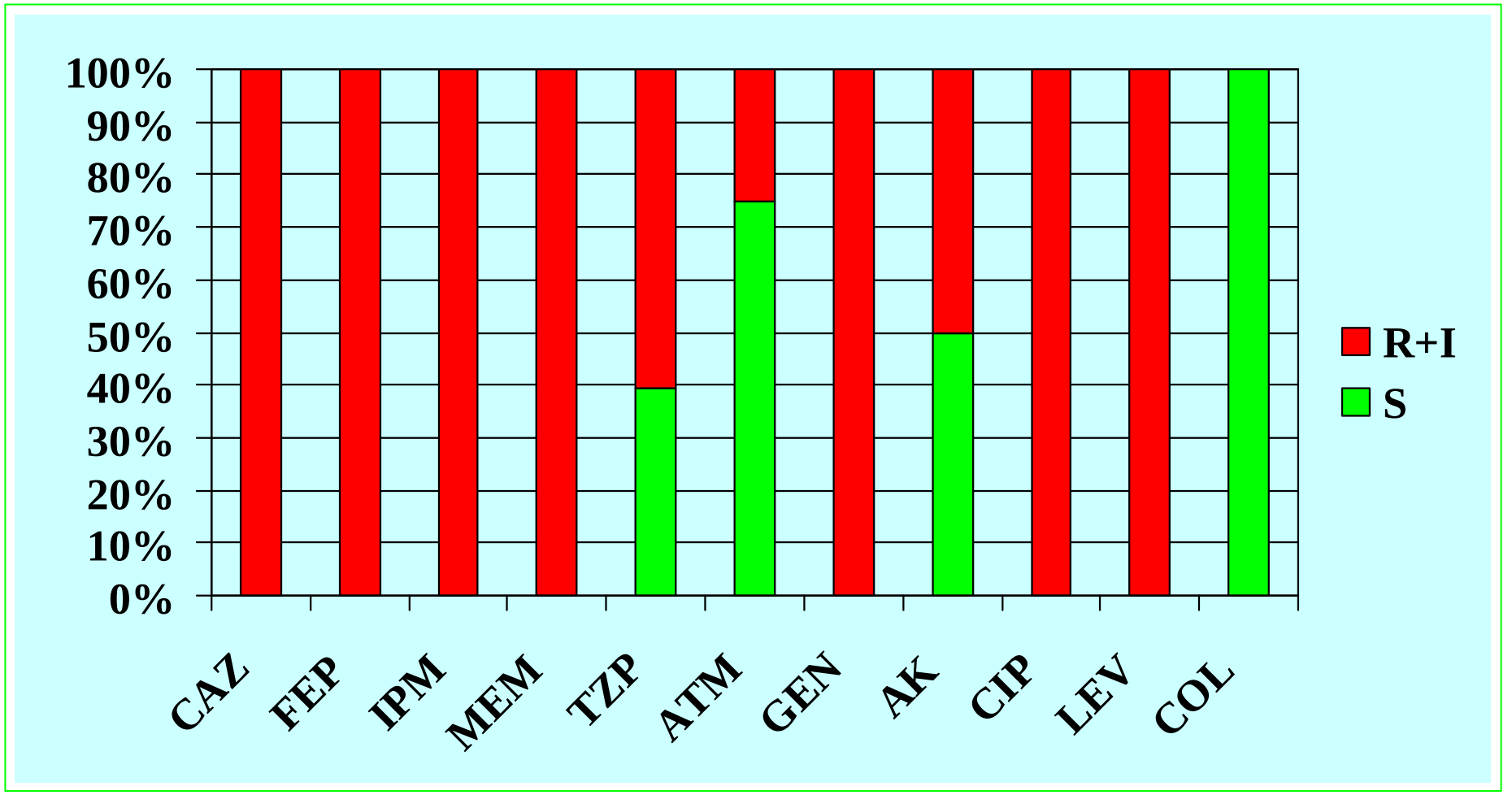


Ps. aeruginosa
resistenza
MULTIPLA

Pseudomonas aeruginosa resistance trends, Italy



Antimicrobial susceptibility of MBL-producing *P. aeruginosa* from the first Italian nationwide survey



Rossolini et al. – unpublished

Terapia delle infezioni da Pseudomonas aeruginosa MDR

1. COLIMICINA (9 milioni dose da carico poi 4,5 milioni x 2 / die)
   +
   RIFAMPICINA 600 -900 mg /die (l'uso prescinde dalla sensibilità in vitro)

2. COLIMICJNA (dose come sopra)
   +
   FOSFOMICINA (4 gr x 4 / die) (solo se è dimostrata una sensibilità in vitro)

3. CEFTAZIME (2 gr x 3 /die),
   CEFEPIME (2 gr x 3 /die),
   PIPERACILLINA/TAZOBACTAM (4 gr x 4 / die),
   IMIPENEM (1 gr x 3-4/die),
   MEROPENEM (1gr x 3-4, 2 gr x 3 /die)
   +
   CIPROFLOXACINA (400 mg x 3 / die)
   oppure
   LEVOFLOXACINA (500 mg x 2 / die)
   oppure
   AMIKACINA (1 gr / die, nelle polmoniti 1,5 gr/die)
   (richiedere studio in vitro di sinergia)

Terapia derivante da test di sinergia in vitro

FOSFOMICINA

- Derivato dell'acido fosfonico isolato nel 1969 da colture di *Streptomyces spp*., attualmente prodotta in <u>forma sintetica</u>
  - fosfomicina-trometamina o fosfomicina sale calcico: **formulazione orale**
  - fosfomicina di-sodica: **formulazione parenterale**

- **Battericida**, inibisce la sintesi di peptidoglicano ad uno stadio più precoce rispetto alle β-lattamine

- **Ampio spettro d'azione**

  <u>- Gram positivi</u>: *S.aureus* anche *MR, S. epidermidis, S.pneumoniae, E.faecalis anche VR*

  <u>- Gram negativi</u>: *E.coli, Proteus spp, K.pneumoniae, Enterobacter spp, Serratia marcescens, Salmonella typhi*

  INATTIVA: *L. monocytogenes, Bacteroides fragilis.*

  Acinetobacter baumannii e *P.aeruginosa* <u>tendenzialmente resistenti</u>, ma se associata ad altre classi antibiotiche può manifestare <u>effetto sinergico</u>

- Meccanismo d'azione **concentrazione-dipendente o tempo-dipendente non chiaro**, secondo alcuni studi
  - concentrazione-dip. per *E.coli, Proteus mirabilis* (vitro) e *S.pneumoniae* (vivo)
  - tempo-dip per *S.aureus* (vitro)

CID 2008;46:1069-77
Int J Antimicrob Agents 2009;34:506-15

Sensibilità alla fosfomicina di Enterobacteriacee ESBL + isolate in corso di infezioni diverse da UTI e tratto gastro-enetrico

	Studies showing susceptibility to fosfomycin of 90% or more compared with total number of studies	Cumulative susceptibility of isolates according to the CLSI criteria†
All Enterobacteriaceae isolates		
Any advanced antimicrobial drug resistance profile	11 of 17 (64·7%)[18-34]	3891 of 4478 (86·9%)[18-25,27,29,31]
ESBL-producing	11 of 17 (64·7%)[18-34]	3569 of 3911 (91·3%)[18-25,27,29,31]
Isolates from urinary tract	8 of 10 (80·0%)[19-21,23-28,30]	2061 of 2227 (92·5%)[19-21,23-25,27]
Isolates from mixed sites‡	5 of 8 (62·5%)[18,21,25,29,31-34]	1508 of 1684 (89·5%)[18,21,25,29,31]
Isolates from outpatients	3 of 3 (100·0%)[20,21,24]	292 of 297 (98·3%)[20,21,24]
Isolates from hospitalised patients	4 of 8 (50·0%)[21,23,25,28,29,31,33,34]	1344 of 1519 (88·5%)[21,23,25,29,31]
***Escherichia coli* isolates**		
Any advanced antimicrobial drug resistance profile	11 of 12 (91·7%)[18,20,21,24-32]	1672 of 1725 (96·9%)[18,20,21,24,25,27,29,31]
ESBL-producing	11 of 12 (91·7%)[18,20,21,24-32]	1604 of 1657 (96·8%)[18,20,21,24,25,27,29,31]
Isolates from urinary tract	6 of 7 (85·7%)[20,21,24-28]	704 of 721 (97·6%)[20,21,24,25,27]
Isolates from mixed sites‡	5 of 6 (83·3%)[18,25,29-32]	900 of 936 (96·2%)[18,25,29,31]
Isolates from outpatients	3 of 3 (100%)[20,21,24]	292 of 297 (98·3%)[20,21,24]
Isolates from hospitalised patients	4 of 5 (80·0%)[21,25,28,29,31]	864 of 909 (95·0%)[21,25,29,31]
***Klebsiella pneumoniae* isolates**		
Any advanced antimicrobial drug resistance profile	3 of 6 (50·0%)[18,21,29-31,33]	608 of 748 (81·3%)[18,21,29,31]
ESBL-producing	3 of 6 (50·0%)[18,21,29-31,33]	608 of 748 (81·3%)[18,21,29,31]
Isolates from mixed sites‡	2 of 5 (40·0%)[18,21,29,31,33]	608 of 748 (81·3%)[18,21,29,31]
Isolates from hospitalised patients	2 of 4 (50·0%)[21,29,31,33]	480 of 610 (78·7%)[21,29,31]

ESBL=extended-spectrum β-lactamase. CLSI=Clinical and Laboratory Standards Institute. *Multidrug resistance, carbapenem-resistance, or production of ESBLs, AmpC β-lactamases, serine carbapenemases, or metallo-β-lactamases. †CLSI fosfomycin susceptibility criteria refer specifically to urinary isolates of *Escherichia coli*. ‡Urinary tract isolates are potentially included.

SUCCESSO CLINICO

Pts trattati 1604
- guariti 81.1%
- migliorati 2.9%

RIDOTTO rischio di selezionare R in corso di trattamento

Lancet Inf Dis 2010;10:43-50

FOSFOMICINA

VIA DI SOMMINISTRAZIONE :	E.V.
DOSE UNITARIA :	4 gr.
PICCO SERICO :	123 ± 16 mg/l
POSOLOGIA:	12-16 gr. in 3-4 dosi
METABOLIZZAZIONE:	assente
LEGAME PROTEICO:	< 10
VOLUME DISTRIBUZIONE:	0,3 l/kg
ESCREZIONE URINARIA:	> 85 %
ELIMINAZIONE BILIARE:	modesta
DIFFUSIONE NEL LCR :	20% dei valori serici

Terapia delle infezioni da Stenotrophomonas maltophilia

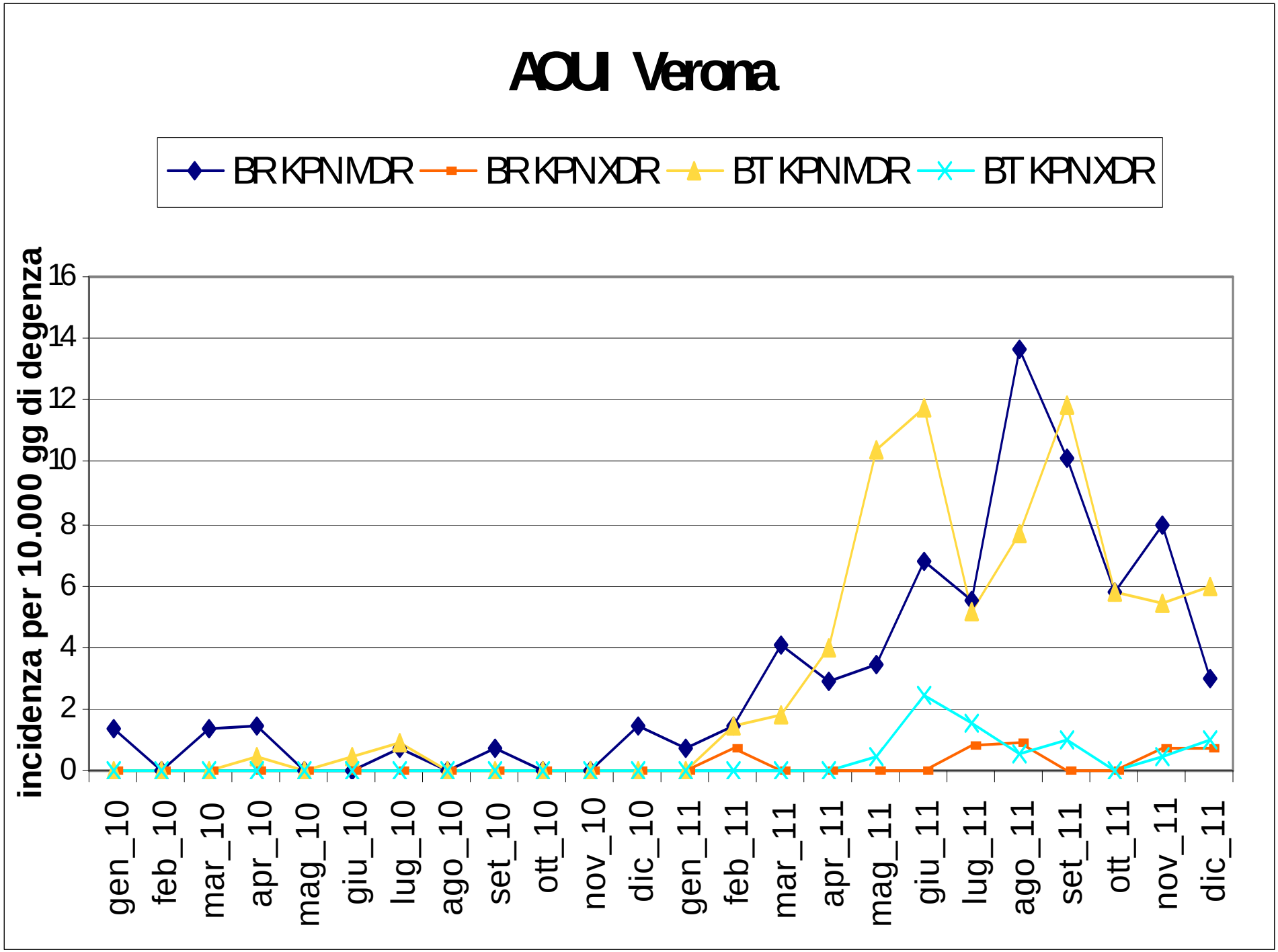
1. COTRIMOXAZOLO 3 fiale (80 mg Trimetoprim x fiala) x 4 / die

2. TICARCILLINA/CLAVULANATO 3,1 gr x 4 / die

3. TIGECICLINA 100 mg poi 50 mg x 2 / die
   (aumentare la dose se scarsa risposta clinica)

Le panresistenze

AOUI Verona


BR KPN MDR
BR KPN XDR
BT KPN MDR
BT KPN XDR
incidenza per 10.000 gg di degenza
0
2
4
6
8
10
12
14
16
gen_10
feb_10
mar_10
apr_10
mag_10
giu_10
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gen_11
feb_11
mar_11
apr_11
mag_11
giu_11
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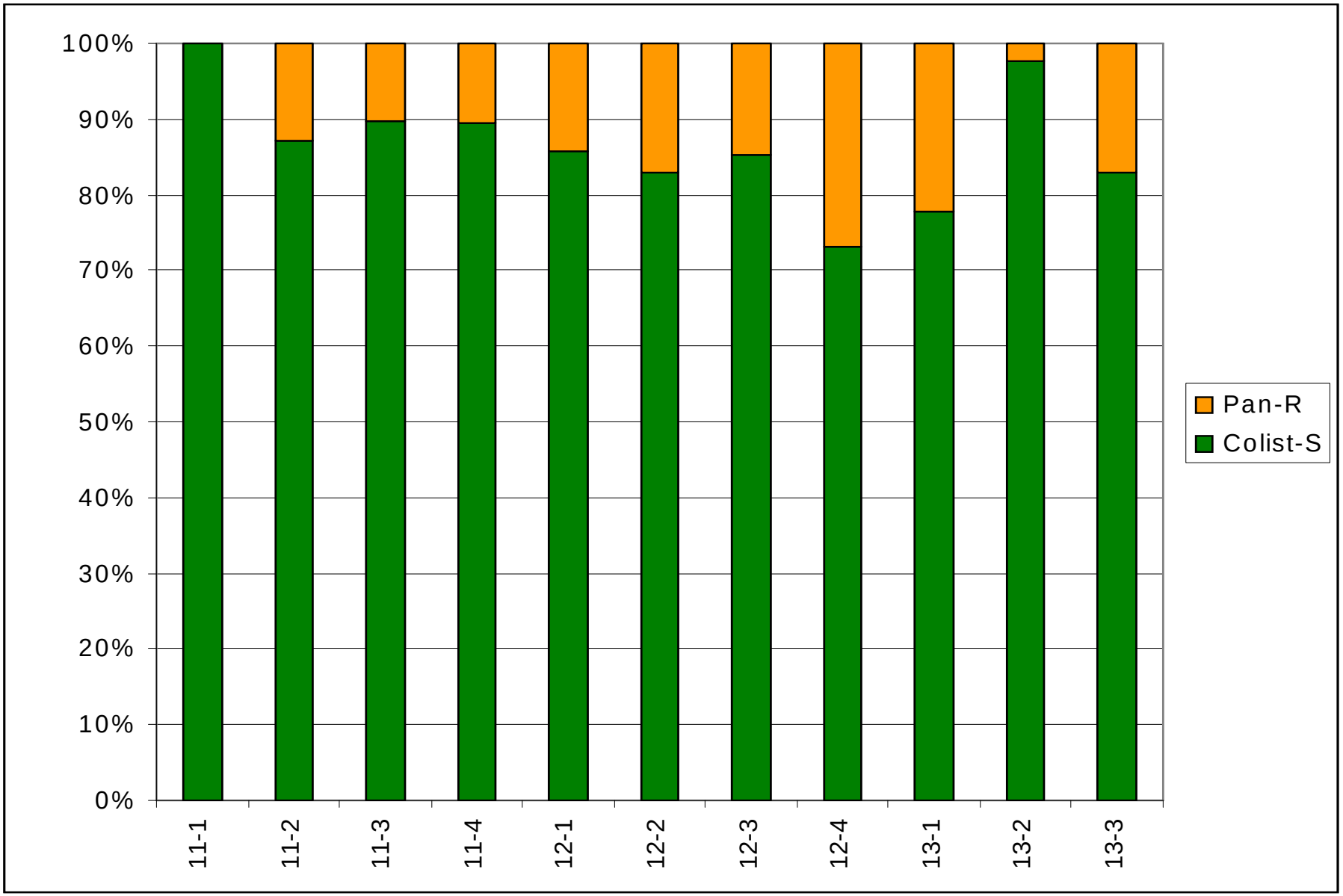
Prevalenza della pan- resistenza tra le CRKP, Osp. B.go Trento, AOUI Verona



Journal of Antimicrobial Chemotherapy (2009) **64**, *Suppl. 1*, i29–i36
doi:10.1093/jac/dkp255

JAC

Has the era of untreatable infections arrived?

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Antibiotic resistance is a major public health concern, with fears expressed that we shortly will run out of antibiotics. In reality, the picture is more mixed, improving against some pathogens but worsening against others. Against methicillin-resistant *Staphylococcus aureus* (MRSA)—the highest profile pathogen—the range of treatment options is expanding, with daptomycin, linezolid and tigecycline all launched, and telavancin, ceftobiprole, ceftaroline and dalbavancin anticipated. There is a greater problem with enterococci, especially if, as in endocarditis, bactericidal activity is needed and the isolate has high-level aminoglycoside resistance; nevertheless, daptomycin, telavancin and razupenem all offer cidal potential. Against Enterobacteriaceae, the rapid and disturbing spread of extended-spectrum β-lactamases, AmpC enzymes and quinolone resistance is forcing increased reliance on carbapenems, with resistance to these slowly accumulating via the spread of metallo-, KPC and OXA-48 β-lactamases. Future options overcoming some of these mechanisms include various novel β-lactamase-inhibitor combinations, but none of these overcomes all the carbapenemase types now circulating. Multiresistance that includes carbapenems is much commoner in non-fermenters than in the Enterobacteriaceae, depending mostly on OXA carbapenemases in *Acinetobacter baumannii* and on combinations of chromosomal mutation in *Pseudomonas aeruginosa*. No agent in advanced development has much to offer here, though there is interest in modified, less-toxic, polymyxin derivatives and in the siderophore monobactam BAL30072, which has impressive activity against *A. baumannii* and members of the *Burkholderia cepacia* complex. A final and surprising problem is *Neisseria gonorrhoeae*, where each good oral agent has been eroded in turn and where there is now little in reserve behind the oral oxyimino cephalosporins, to which low-level resistance is emerging.

Keywords: β-lactamases, MRSA, *Escherichia coli*, *Acinetobacter baumannii*, *Neisseria gonorrhoeae*

Antimicrobial Agents Chemotherapy C.C: Bulik 2011

DOUBLE-CARBAPENEM THERAPY FOR CARBAPENEMASE-PRODUCING KLEBSIELLA PNEUMONIAE (ERTAPENEM + DORIPENEM)

Paziente di anni 65 affetta da cirrosi su base alcolica ed insufficienza renale cronica venne sottoposta a **trapianto di fegato** a settembre 2012.

Nei giorni successivi al trapianto sviluppò un quadro settico da E. faecium; trattata con adeguata terapia antibiotica gradualmente migliorò e fu dimessa 46 giorni dopo il trapianto.

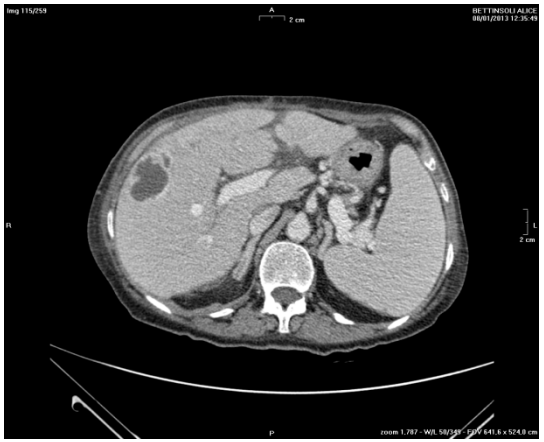
Dai tamponi di sorveglianza fu isolata una KPC

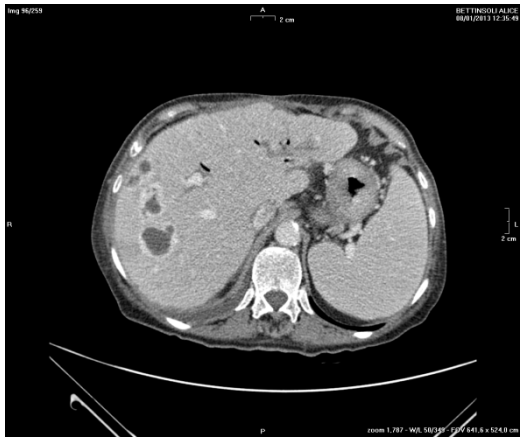
Fu nuovamente ricoverata alla fine di dicembre per insorgenza di quadro settico. Una TAC dell'addome rilevò una presenza di **multipli ascessi epatici** il maggiore di 3,5 cm. Di diametro. Le emoculture risultarono positive sia per E. coli che per KPC; iniziò una terapia con Meropenem, Tigeciclina e Gentamicina.

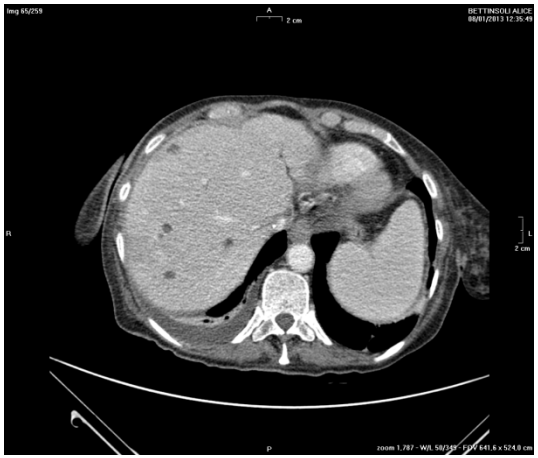
Le due lesioni maggiori furono drenate per via percutanea. Il ceppo isolato di K. Pneumoniae risultò ***panresistente***. Si instaurò terapia con ***Ertapenem + Meropenem***. Una PET TAC eseguita dopo un mese evidenziò un netto miglioramento. Un nuovo esame eseguito dopo tre mesi rilevò un ulteriore miglioramento.

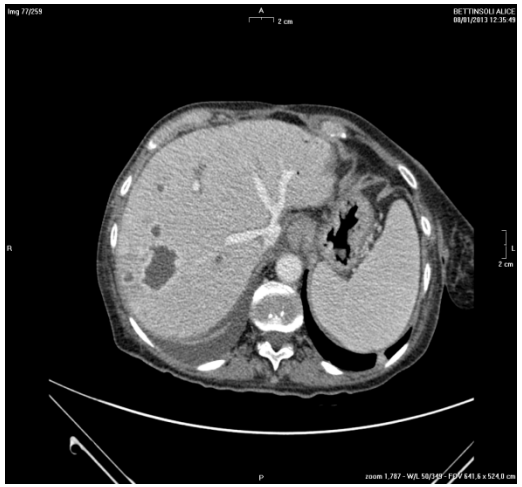
Attualmente la paziente, da più di 4 mesi dalla sospensione della terapia è a domicilio senza segni di infezione.

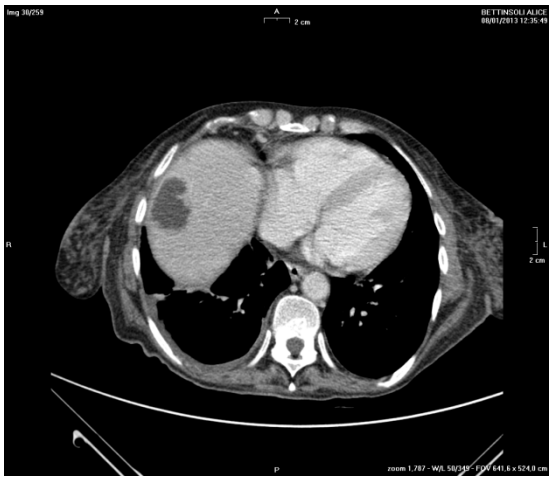
TAC Addome 8/01/13



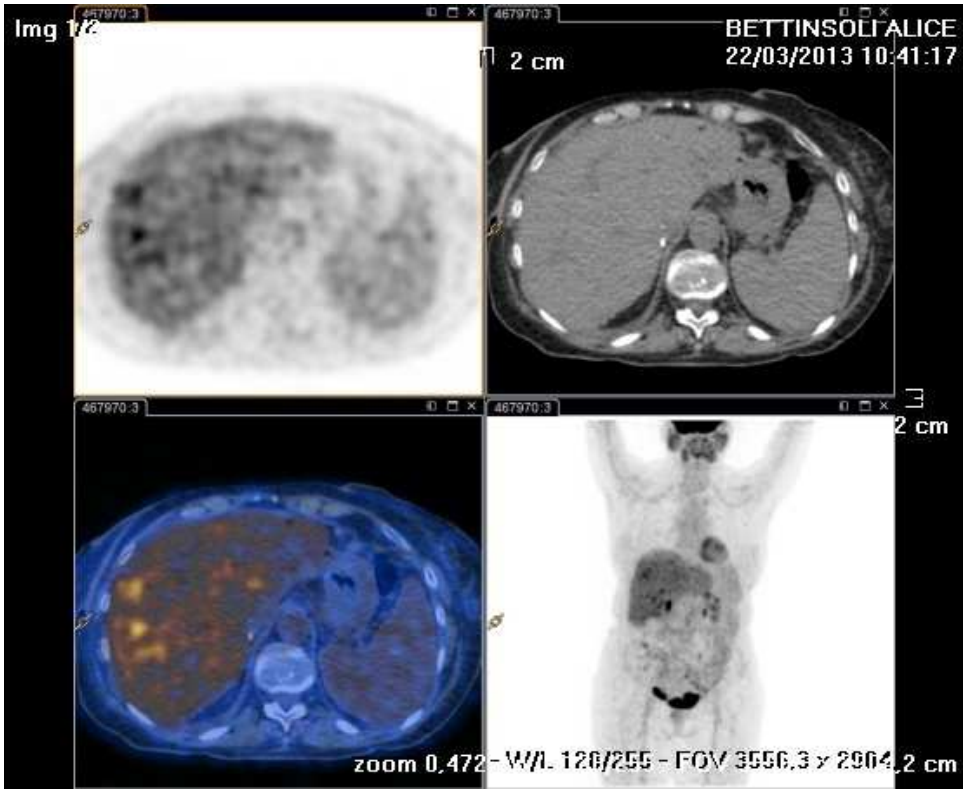








PET-TAC
22/03/13



La tomografia per emissione di positroni, eseguita con apparecchiatura PET-TC time of flight e scansioni dalla base cranica alla radice delle cosce un'ora dopo la somministrazione del fluorodesossiglucosio in presenza di valori di glicemia pari a 89 mg/dl, evidenzia discreta riduzione del metabolismo glucidico nelle note areole ascessuali epatiche. Attualmente si rileva moderata captazione in area mal definita alla TC di repere tra VII e VI segmento epatico (SUV max 5.2 vs 10.7), mentre non sono più apprezzabili metabolicamente le altre areole ubiquitarie nel fegato.
Non altre aree di aumentato metabolismo glucidico a livello dei restanti distretti corporei esaminati.

CONCLUSIONI: buona rispota alla terapia con modesto residuo ascessuale tra VI e VII segmento epatico

CONSIDERAZIONI FINALI

1. Fenomeno irreversibile
2. Uso corretto e limitato degli antibiotici (terapia-profilassi)
3. Precauzioni universali per il controllo della trasmissione (lavaggio mani, precauzioni standard e da contatto, isolamento respiratorio e/o da contatto, strumentazioni ecc…)
4. Screening? (malato proveniente da RSA)
5. Mobilità all'interno dell'ospedale
6. Dimissioni precoci
7. Scheda paziente
8. Non abituarsi all'emergenza

NUOVI ANTIBIOTICI

Table 1. Activity of β-lactamase inhibitors

β-Lactamase	Inhibitor (IC_{50} μM)		
	Tazobactam	Avibactam	MK7655
TEM-1	0.01	0.01	0.03
KPC-2	43.00	0.17	0.21
SHV-1	0.07	NR	0.03
SHV-4	0.06	0.003	NR
SHV-5	0.01	NR	0.36
CTX-M15	0.01	0.01	NR
AmpC (*P. aeruginosa*)	1.49	0.13	0.47
P99	12.00	0.10	0.13
Oxa (*A. baumannii*)	58.00	NR	>50

Adapted from Refs. 8–10.
NR = not reported.

D M Shales 2013

Table 3. Antimicrobial activity of β-lactam–β-lactamase inhibitor combinations against key pathogens[15,19–23]

Pathogen	Ceftazidime	Ceftazidime–avibactam	Ceftaroline	Ceftaroline–avibactam	Ceftolozane	Ceftolozane–tazobactam	(MIC$_{90}$ μg/mL) Imipenem	Imipenem-MK7655
E. coli ESBL	32	0.5	>32	0.25	>32	16		
K. pneumoniae ESBL	>32	2	>32	1	>32	>16		
K. pneumoniae NS to carbapenem	>32	2	>32	2	>32	>16	64	1
E. cloacae Ceftazidime-R	>32	2	>32	1	>32	>16		
Enterobactereaceae Multiple β-lactamases	>256	4	>64	0.5				
CTX-M (538)			>32	0.25				
KPC (118)			>32	1				
SHV (50)			>32	0.5				
AmpC + CTX-M (43)			>32	2				
SHV + CTX-M (28)			>32	0.25				
SHV + KPC (18)			>32	4				
Pseudomonas aeruginosa	32	8	Not expected	Not expected	8	8	32	4

Blank cell = not reported. Not expected = not expected to be active.

D M Shales 2013

NXL-104 (Avibactam)

- NXL-104 (Novexel, now AstraZeneca) is a non-β-lactam β-lactamase inhibitor .
- It restores β-lactam activity against Enterobacteriaceae producing:
  - class A enzymes (including many ESBLs)
  - class C enzymes (derepressed AmpC)
  - some class D enzymes
- NXL-104 is <u>not active</u> against class-B enzyme producers.

Table 3 continued

	β-lactamase enzyme[a]	MIC		MIC reduction (fold)
		Ceftazidime	Ceftazidime-avibactam[b]	
Klebsiella pneumoniae				
Extended-spectrum β-lactamases	CTX-M-3	16	0.5	32
	CTX-M-14	16	1	16
	CTX-M-15[c]	>128	1	>128
	SHV-2	>64	0.5	>128
	SHV-3	>64	0.5	>128
	SHV-4	>256	4	>64
	SHV-5	64	0.5	128
	SHV-6	4	1	4
	SHV-18	64	2	32
	SHV-38	8	2	4
	TEM-4	32	0.5	64
	CTX-M-2, TEM-1B	128	2	64
	CTX-M-16, OXA-1	256	1	256
	SHV-5, TEM-10	>128	2	>64
	CTX-M-2, SHV-5, TEM-12	>128	2	>64
	CTX-M-2, SHV-2, TEM-12	>128	4	>32
	CTX-M-3, SHV-1, TEM-1B	256	2	128
	CTX-M-15, TEM-1, OXA-1	256	2	128
	SHV-1, TEM-2, PER	256	4	64
Carbapenemases	KPC-2[c]	>128	1	>128
	KPC-3[c]	256	0.5	512
	KPC-2, SHV-11, SHV-12, TEM-1	512	≤0.06	≥8192
Metallo-β-lactamases	VIM-1, SHV-5	256	256	1
Ambler class C β-lactamases	AmpC + SHV-11	64	2	32
	DHA-2	256	2	128
	ACC-1, TEM-1	128	1	128
	LAT-4, SHV-11 variant	32	1	32
	CMY-4, TEM-1	256	0.5	512
	DHA-1, SHV-2a, TEM-1	>128	1	>128
	MOX-2, SHV-5, TEM-1	256	1	256

[a] Isolates may contain genes encoding other β-lactamases

[b] Fixed avibactam concentration of 4 mg/L

[c] Modal MIC values derived from MIC data for ten or more unique isolates

MIC minimum inhibitory concentration

DRUGS 2013

11 Place of Ceftazidime/Avibactam in Therapy

The addition of avibactam restores the activity of ceftazidime against Gram-negative bacilli that achieve β-lactam resistance through expression of the Ambler class A ESBLs, chromosomal or mobile class C β-lactamases, serine carbapenemases, or some class D β-lactamases. Safety and pharmacokinetic results published to date suggest that no additional considerations need to be taken when dosing ceftazidime-avibactam compared with ceftazidime alone. Ceftazidime-avibactam has demonstrated clinical efficacy similar to that of carbapenem therapy in phase II studies of complicated intra-abdominal infection and complicated urinary tract infection (including acute pyelonephritis). The extensive clinical experience with ceftazidime and the knowledge that avibactam broadens the spectrum of ceftazidime versus ß-lactamase-producing Gram-negative bacilli, will provide clinicians with confidence in using this agent. To date, no data are available on the efficacy of ceftazidime-avibactam for the treatment of difficult-to-treat infections such as hospital-acquired and ventilator-acquired pneumonia. The exact roles for ceftazidime-avibactam in the treatment of infectious diseases will, in part, depend on the development of other β-lactam/β-lactamase inhibitor combinations including ceftaroline-avibactam, imipenem-MK7655 and ceftolozane-tazobactam. An important advantage of ceftazidime-avibactam is that its development is furthest along and it may be first to market.

Potential future roles for ceftazidime-avibactam include the treatment of suspected or documented infections caused by resistant Gram-negative bacilli-producing ESBL, KPC and/or AmpC β-lactamases. In addition, ceftazidime-avibactam may be used in combination (with metronidazole) for suspected polymicrobial infections. Finally, the increased activity of ceftazidime-avibactam versus *P. aeruginosa* may be of clinical benefit in patients with suspected or documented *P. aeruginosa* infections.

DRUGS 2013

MK-7655

- **MK-7655 is a novel compound active against class A and class C carbapenemases with a good in vitro and in vivo activity in combination with imipenem**
- In a phase I randomized, double-blind, placebo-controlled study, MK-7655 was shown to have a favorable pharmacokinetics profile when administered in combination with cilastatin and imipenem.

Possibili siti di contaminazione

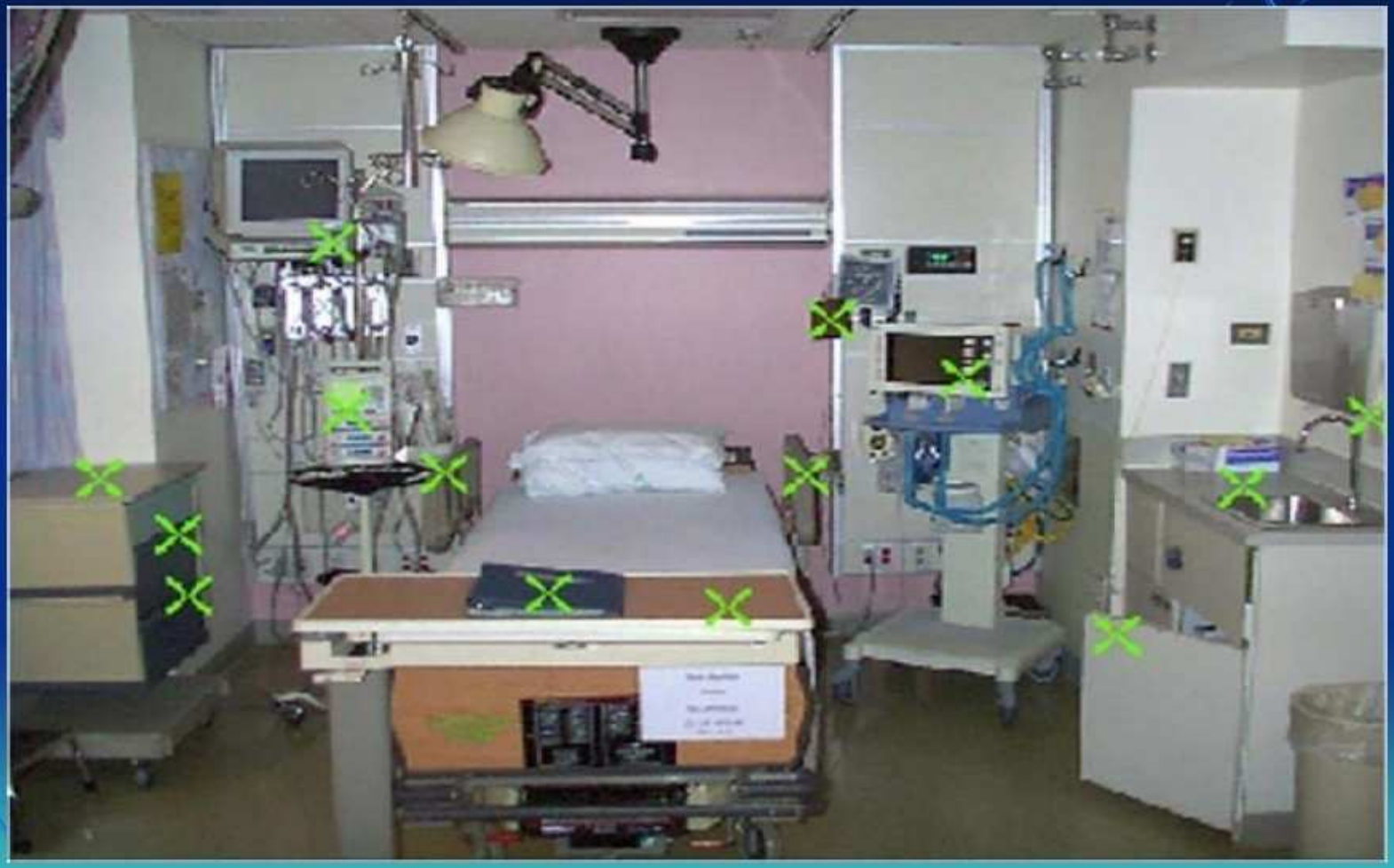
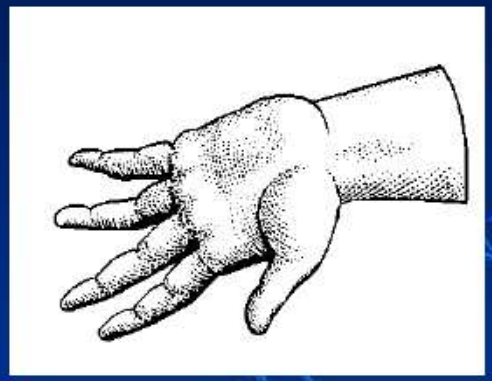


Table 1: Persistence of clinically relevant bacteria on dry inanimate surfaces.

Type of bacterium	Duration of persistence (range)	Reference(s)
Acinetobacter spp.	3 days to 5 months	[18, 25, 28, 29, 87, 88]
Bordetella pertussis	3 – 5 days	[89, 90]
Campylobacter jejuni	up to 6 days	[91]
Clostridium difficile (spores)	5 months	[92–94]
Chlamydia pneumoniae, C. trachomatis	≤ 30 hours	[14, 95]
Chlamydia psittaci	15 days	[90]
Corynebacterium diphtheriae	7 days – 6 months	[90, 96]
Corynebacterium pseudotuberculosis	1–8 days	[21]
Escherichia coli	1.5 hours – 16 months	[12, 16, 17, 22, 28, 52, 90, 97–99]
Enterococcus spp. including VRE and VSE	5 days – 4 months	[9, 26, 28, 100, 101]
Haemophilus influenzae	12 days	[90]
Helicobacter pylori	≤ 90 minutes	[23]
Klebsiella spp.	2 hours to > 30 months	[12, 16, 28, 52, 90]
Listeria spp.	1 day – months	[15, 90, 102]
Mycobacterium bovis	> 2 months	[13, 90]
Mycobacterium tuberculosis	1 day – 4 months	[30, 90]
Neisseria gonorrhoeae	1 – 3 days	[24, 27, 90]
Proteus vulgaris	1 – 2 days	[90]
Pseudomonas aeruginosa	6 hours – 16 months; on dry floor: 5 weeks	[12, 16, 28, 52, 99, 103, 104]
Salmonella typhi	6 hours – 4 weeks	[90]
Salmonella typhimurium	10 days – 4.2 years	[15, 90, 105]
Salmonella spp.	1 day	[52]
Serratia marcescens	3 days – 2 months; on dry floor: 5 weeks	[12, 90]
Shigella spp.	2 days – 5 months	[90, 106, 107]
Staphylococcus aureus, including MRSA	7 days – 7 months	[9, 10, 16, 52, 99, 108]
Streptococcus pneumoniae	1 – 20 days	[90]
Streptococcus pyogenes	3 days – 6.5 months	[90]
Vibrio cholerae	1 – 7 days	[90, 109]

Ruolo delle mani nella trasmissione delle infezioni ospedaliere

LA MANO PRENDE
- dalla cute
- dalle ferite infette
- dal pus
- dalle secrezioni



- dalla faccia
- dal corpo
- dalle mani
- dai vestiti

del paziente

del personale sanitario

LA MANO INFETTA
- pazienti operati
- bambini
- malati gravi
- malati cronici
- anziani
- personale sanitario

LA MANO TRASFERISCE
- alle lenzuola
- alla biancheria sporca
- agli asciugamani umidi
- a bacinelle e lavandini
- ai bagni

LA MANO CONTAMINA
- attrezzature sanitarie
- biancheria pulita
- bagni
- piatti e posate
- etc.

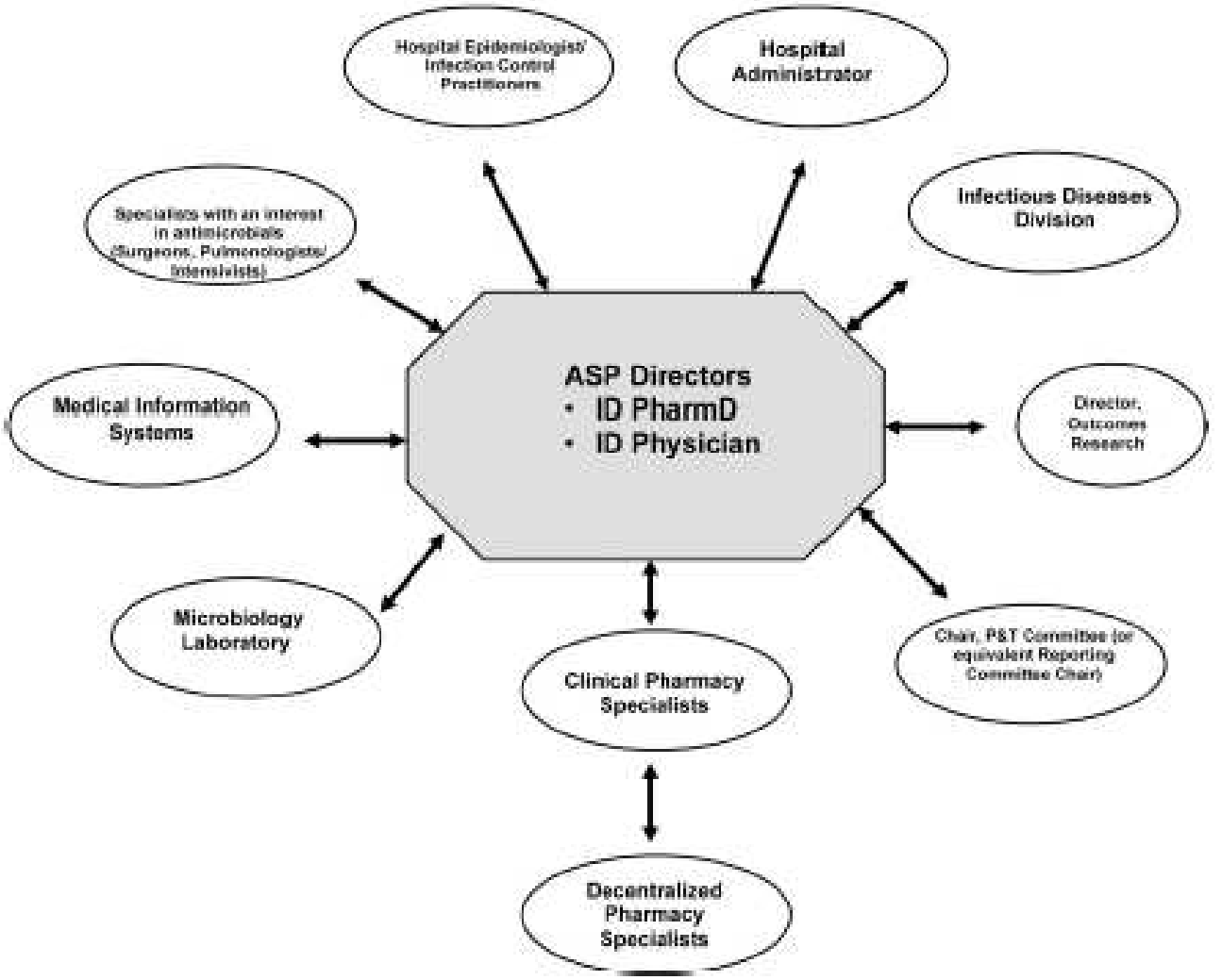
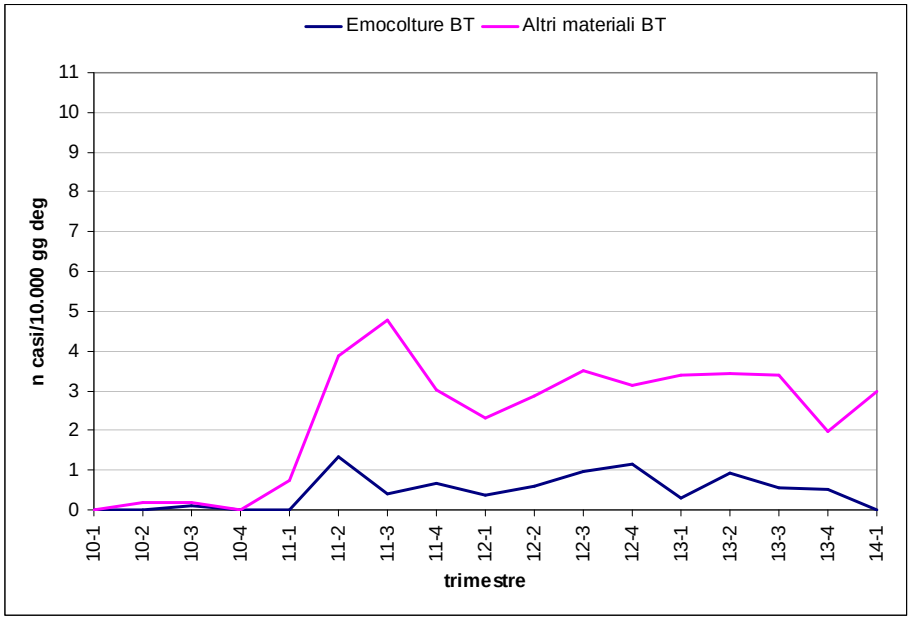


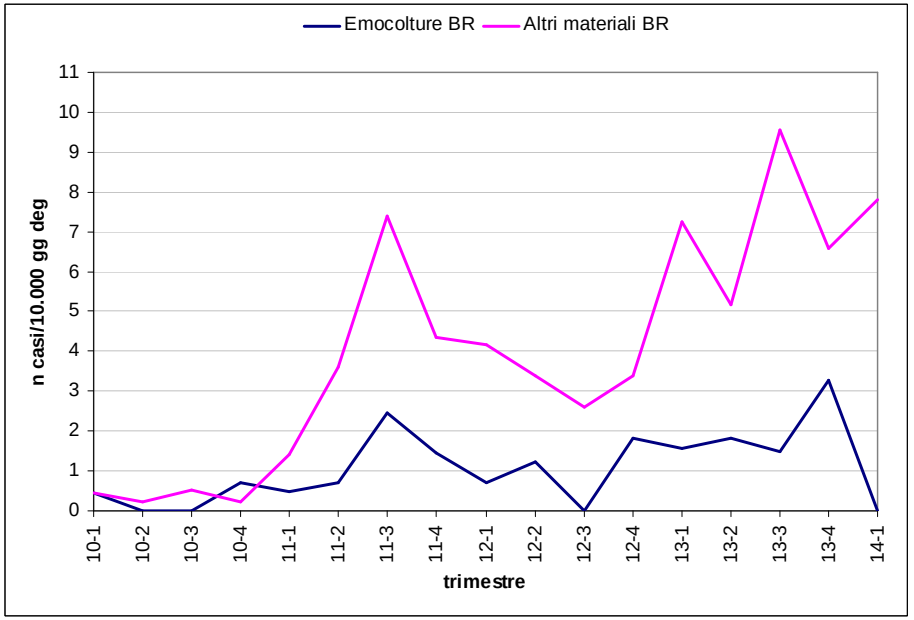
Fig. 6. Multidisciplinary involvement and core team members for a larger hospital. Smaller hospitals need the same core members but may not have some of the groups listed.

Incidenza di *K. pneumoniae* produttore di carbapenemasi presso i presidi ospedalieri dell'AUOI di Verona, 2010-2014*

Osp. Borgo Trento

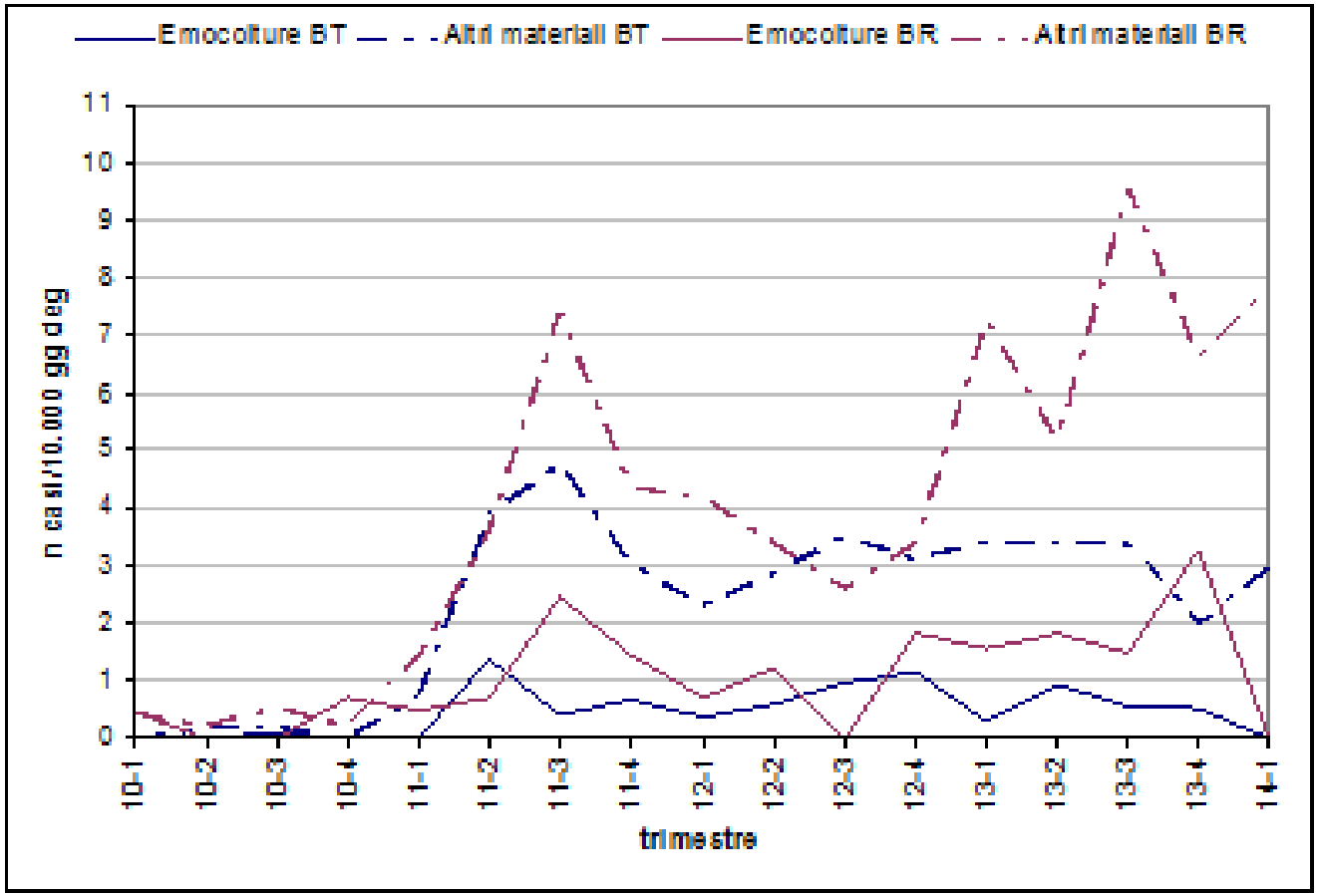


Osp. Borgo Roma



* fino al 28 febbraio 201

Incidenza di *K. pneumoniae* produttore di carbapenemasi presso i presidi ospedalieri dell'AUOI di Verona, 2010-2014*



* fino al 28 febbraio 2014

CURRENT OPINION

Azole resistance in *Aspergillus fumigatus*: a growing public health concern

Edith Vermeulen[a], *Katrien Lagrou*[a,b], *and Paul E. Verweij*[c]

Purpose of review

Reports from the end of the 2000s forced the medical community to take azole resistance in *Aspergillus fumigatus* into account. Not only patients with chronic aspergillus disease, who develop resistance during long-term azole treatment, but also azole-naive patients are at risk, owing to the presence of resistant strains in the environment. The purpose of this review is to overview the latest findings concerning the origin, evolution, and implications of azole resistance in *A. fumigatus*.

Recent findings

TR_{34}/L98H is the predominant resistance mechanism of environmental origin in *A. fumigatus*. Recent epidemiological data show that this mechanism is an expanding problem, with reports from China, Iran, and India. However, the TR_{34}/L98H strains from the Middle East are genotypically different from the European isolates; their emergence is, therefore, not due to simple geographical spread of the 'European' isolates. A new environmental resistance mechanism, TR_{46}/Y121F/T289A, was detected in the Netherlands, conferring voriconazole resistance. In patients chronically treated with triazoles, the spectrum of resistance has become more diverse, with the emergence of non-*CYP51A*-mediated mechanisms. Central registration of treatment and outcome data of patients with resistant aspergillus disease are needed.

Summary

Azole resistance in *A. fumigatus* is evolving to a global health problem.

Keywords

aspergillosis, *Aspergillus fumigatus*, CYP51A, drug resistance, fungal

Table 1. Rate of resistant isolates among clinical *Aspergillus fumigatus* isolates and prevalence of resistance in colonized or infected patients

Country, ref.	Study period	Study isolates	Resistance rate	Resistance prevalence	TR_{34}/L98H rate	TR_{34}/L98H prevalence
UK, [6]	1997–2007	Clinical isolates, irrespective of relevance; referral center for chronic/allergic aspergillosis	34/519 (6.6%)	20/400 (5%)	2/519 (0.4%)	2/400 (0.5%)
UK, [8]	2008–2009	Clinical isolates sent for susceptibility testing; referral center for chronic/allergic aspergillosis	64/230 (27.8%)	28/157 (17.8%)	0/230 (0%)	0/157 (0%)
The Netherlands, [12]	1994–2007	Clinical isolates, irrespective of relevance	63/2061 (3.1%)	45/1320 (3.4%)	–	39/1320 (3.0%)
The Netherlands, [13]	2007–2009	Clinical isolates, irrespective of relevance	82/1792 (4.6%)	63/1192 (5.3%)	74/1792 (4.1%)	57/1192 (4.8%)
The Netherlands, [14▪]	2009–2011	Clinical isolates, irrespective of relevance	–	63/921 (6.8%)	–	47/921[a] (5.1%)
Spain, [15]	2010–2011	Clinical isolates, irrespective of relevance	1/156 (0.6%)	–	–	–
Spain, [16▪]	1999–2011	Clinical isolates from proven or probable invasive aspergillosis or aspergilloma	6/343 (1.8%)	6/148 (4.1%)	0/343 (0%)	0/150 (0%)
Denmark, [10]	2007–2009	Clinical isolates from cystic fibrosis patients, irrespective of relevance	–	6/133 (4.5%)	–	2/133 (1.5%)
France, [17]	2006–2009	Clinical isolates from patients with hematological malignancy, irrespective of relevance	1/118 (0.8%)	1/89 (1.1%)	0/118 (0%)	0/89 (0%)
France, [11]	2010–2011	Clinical isolates from cystic fibrosis patients, irrespective of relevance	–	6/131 (4.6%)	–	2/131 (1.5%)
France, [18▪▪]	2010–2011	Clinical isolates from cystic fibrosis patients, irrespective of relevance	9/85 (10.6%)	4/50 (8.0%)	5/85 (5.9%)	3/50 (6%)
Germany, [19▪]	2011–2012	Clinical isolates irrespective of relevance	3.2% (17/527)	–	6/527 (1.1%)	–
Japan, [20▪]	1994–2010	Clinical isolates, irrespective of relevance (obtained from Pneumology Dept.)	11.2% (22/196)	–	0/196 (0%)	–
India, [21▪]	2005–2010	Clinical isolates from patients suspected of bronchopulmonary aspergillosis	2/103 (1.9%)	2/85 (2.4%)	2/103 (1.9%)	2/85 (2.4%)
Iran, [22▪]	2003–2009	Clinical isolates obtained from patients with aspergillus diseases	3.2% (4/124)	–	3/124 (2.4%)	–
USA, [23]	2001–2006	Isolates recovered from transplant recipients with proven or probable invasive aspergillosis	1/181 (0.6%)	–	–	–

Resistance rate: resistant isolates/all isolates tested; resistance prevalence: percentage of patients with a resistant strain among patients with *Aspergillus fumigatus* from a clinical sample (corrected for repeat sampling); TR_{34}/L98H rate: isolates with *CYP51A* mutation TR_{34}/L98H/all isolates tested; TR_{34}/L98H prevalence: percentage of patients with a resistant strain due to TR_{34}/L98H among patients with *A. fumigatus* from a clinical sample (corrected for repeat sampling).
[a]Thirteen of 921 resistant strains (1.4%) were attributable to the new environmental resistance mechanism TR_{46}/Y121F/T289A.

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