Sistema Socio Sanitario
Ospedale Niguarda
Regione Lombardia

Massimo Puoti
Infectious Diseases – Lab Depts
ASST GRANDE OSPEDALE
METROPOLITANO NIGUARDA
MILANO

INFEZIONI RESPIRATORIE: COSA C'E' DI NUOVO

I batteri multiresistenti

PNEUMOLOGIA 2018

Milano, 14 – 16 giugno 2018 · Centro Congressi Palazzo delle Stelline

INFEZIONI RESPIRATORIE COSA C'E' DI NUOVO: I BATTERI MULTIRESISTENTI

- Antibioticoresistenza un tema d'attualità
- Antibioticoresistenza e consumo/politica degli antibiotici → antimicrobial stewardship in pneumonia
- Nuovi farmaci per la gestione di MDR
  - Gram positivi
  - Gram negativi
    - Grmi produttori di Carbapenemasi
    - Psudomonas multiresistente

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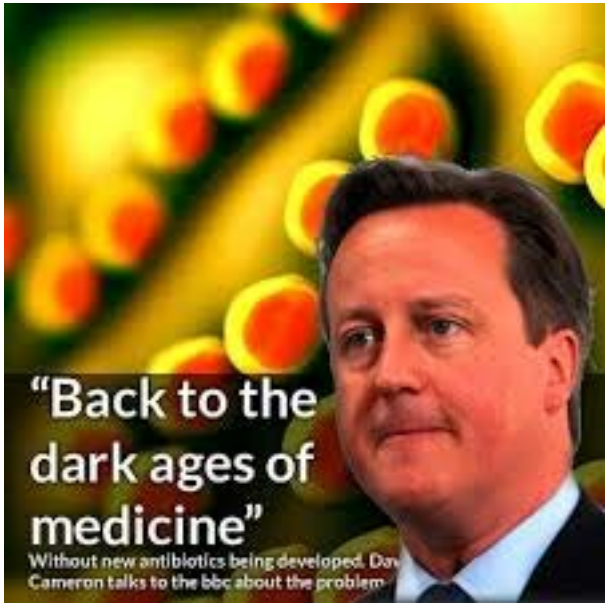
The **White House** has authorized a 5-year National Action Plan to address antibiotic resistance and develop new antibiotics[4]



EUROPEAN ANTIBIOTIC AWARENESS DAY

Conclusions

During conversations in Italy, ECDC often gained the impression that these high levels of AMR appear to be accepted by stakeholders throughout the healthcare system, as if they were an unavoidable state of affairs.

The factors that contribute negatively to this situation seem to be:

- Little sense of urgency about the current AMR situation from most stakeholders and a tendency by many stakeholders to avoid taking charge of the problem;
- Lack of institutional support at national, regional and local level;
- Lack of professional leadership at each level;
- Lack of accountability at each level;
- Lack of coordination of the activities between and within levels.

If the current trends of carbapenem resistance and colistin resistance in gram-negative bacteria such as *Klebsiella pneumoniae* and *A. baumannii* are not reversed, key medical interventions will be compromised in the near future.

Untreatable infections following organ transplantation, intensive care or major surgical interventions are now a significant possibility in many Italian hospitals

Recommendations

Based on these observations, ECDC's team recommends the following actions:

Designate AMR as a national public health threat. The Ministry of Health should formally designate AMR as a national public health threat that affecting all regions. This state of affairs requires prioritisation of resource allocation and short/long term planning.

National Action Plan. The National Action Plan offers an opportunity to design an effective roadmap to achieve these goals. It should be finalised and strengthened as a matter of urgency by including actions, indicators and targets, with measurable outcomes and much shorter deadlines for its operational implementation.

Learn lessons from the recent national vaccination initiative. In the same manner, key performance indicators and targets for AMR should be identified and incorporated into the minimum levels of assistance.

Estimate costs for activities at both national and regional level to make available the appropriate budgets.

The regions with the greatest AMR challenges also tend to be those subjected to the repayment plan. Despite the financial situation, investment into antibiotic stewardship and infection prevention and control has been proven to be cost-effective and will (relatively quickly) result in savings that exceed the amount invested. Financial deficits should not therefore be a barrier to implementation of the National Action Plan and its activities.

Intersectoral Coordinating Mechanism. The Intersectoral Coordinating Mechanism under the Ministry of Health should have a clear mandate that goes beyond completion of the National Action Plan, and receive financial support for its activities.

Appointment of regional AMR specialists. Each region should formally appoint an expert with specialist knowledge of AMR control and clear terms of reference responsible for initiating and coordinating the necessary AMR prevention and control activities. These trained specialists should meet quarterly in an inter-regional assembly to share good practices and support one another.

Central supervision. The heterogeneity of the regional system requires a level of supervision coordinated at a central level. This could take the form of a team of auditors or peer-reviewers who would regularly visit the regions to assess and check that activities are implemented at regional level according to the National Action Plan.

Milestones linked to financial incentives. The achievement of agreed milestones should be linked to financial incentives in order to acknowledge progress and motivate further improvement. Achievement of milestones should be publicised to retain focus and initiative.

At central level, these initiatives are sufficiently significant to justify setting up an adequately resourced team within the Ministry of Health dedicated solely to tackling AMR. This will allow a consistent and uninterrupted level of activity as well as the development of an effective system that provides guidance and audits progress in the regions. The team would also coordinate national and regional public awareness campaigns.

Improve central collection of surveillance data. The surveillance data on AMR and antimicrobial use that is collected centrally needs to be improved. This can be done by improving the geographical representativeness and timeliness of the MICRONET system. In addition, notification of new cases of CRE and MRSA bacteraemia should become mandatory and be undertaken through a simple online reporting system that automatically transmits the information in real time both to the regional and central coordinating entities.

Tackle unaccredited microbiology laboratories. The substantial number of unaccredited microbiology laboratories should be tackled by introducing a programme of minimal accreditation criteria for laboratories that perform analysis of microbiological samples. This intervention would ensure quality results and maximise the effectiveness of the subsequent antibiotic treatments.

Agree minimal structural indicators for effective infection prevention and control and antimicrobial stewardship at hospital level, linked to bed occupancy and type of care provided. This will ensure that the necessary staff are involved at local level. Clear job descriptions and responsibilities should be included.

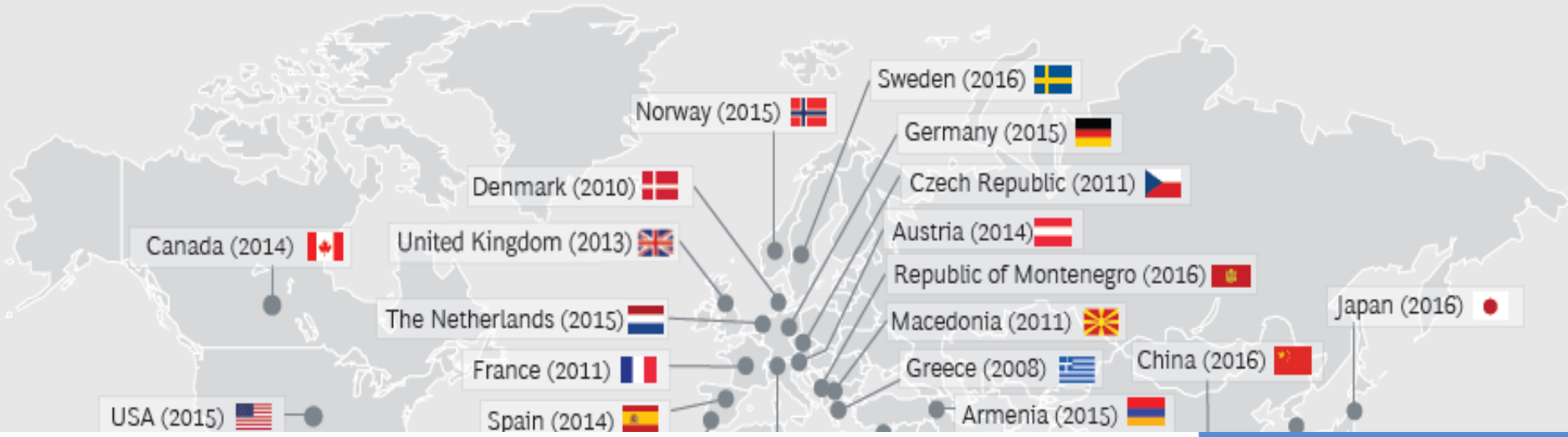
Increase the number of hospital professionals specialising in infection prevention and control and antimicrobial stewardship and the resources for training them.

Publish national guidelines on the use of antibiotics. Italy would benefit greatly from developing and publishing national guidelines with general principles on the use of antimicrobial agents in human medicine.

Check the appropriateness of antibiotics dispensed at pharmacies. In all regions of the country the appropriateness of the antibiotics dispensed at community pharmacies should be checked to establish whether and to what extent antibiotics are being sold over-the-counter without medical prescriptions.

Organise a national antibiotics awareness campaign. Given the Italian population's low level of awareness concerning antibiotics and AMR, Italy would also benefit greatly from the organisation of a national antibiotic awareness campaign on the prudent use of antibiotics. In addition, national communication strategies on the prudent use of antibiotics would benefit from a higher level of cooperation in the regions.

FIGURE 2 | National action plans on antimicrobial resistance (AMR) across the globe



Piano Nazionale di Contrasto dell'Antimicrobico-Resistenza (PNCAR)

2017-2020

Obiettivi nazionali e regionali 2018- 2020

Source: *Antimicrobial Resistance. Library of National Action Plans.* World Health Organization (WHO), 2017

1. Primo piano nazionale italiano
2. Definisce chiaramente obiettivi per ridurre AMR
3. Numerosi riferimenti a indicazioni europee
4. Focalizza sia su comunita` che strutture di cura
5. Parte significativa su obiettivi in ambito veterinario e di sicurezza degli alimenti e degli ambienti

1. Mancanza di definizione di una leadership della stewardship (antibiotica, microbiologica e igiene) a livello ospedaliero
2. Senza controlli di qualita’ alto rischio di incremento di antibiotici non monitorizzati o di uso inappropriato di metodiche costose non basate sull’evidenza
3. Assenza di fondi dedicati chiari
4. Mancanza di investimenti in fondi di ricerca

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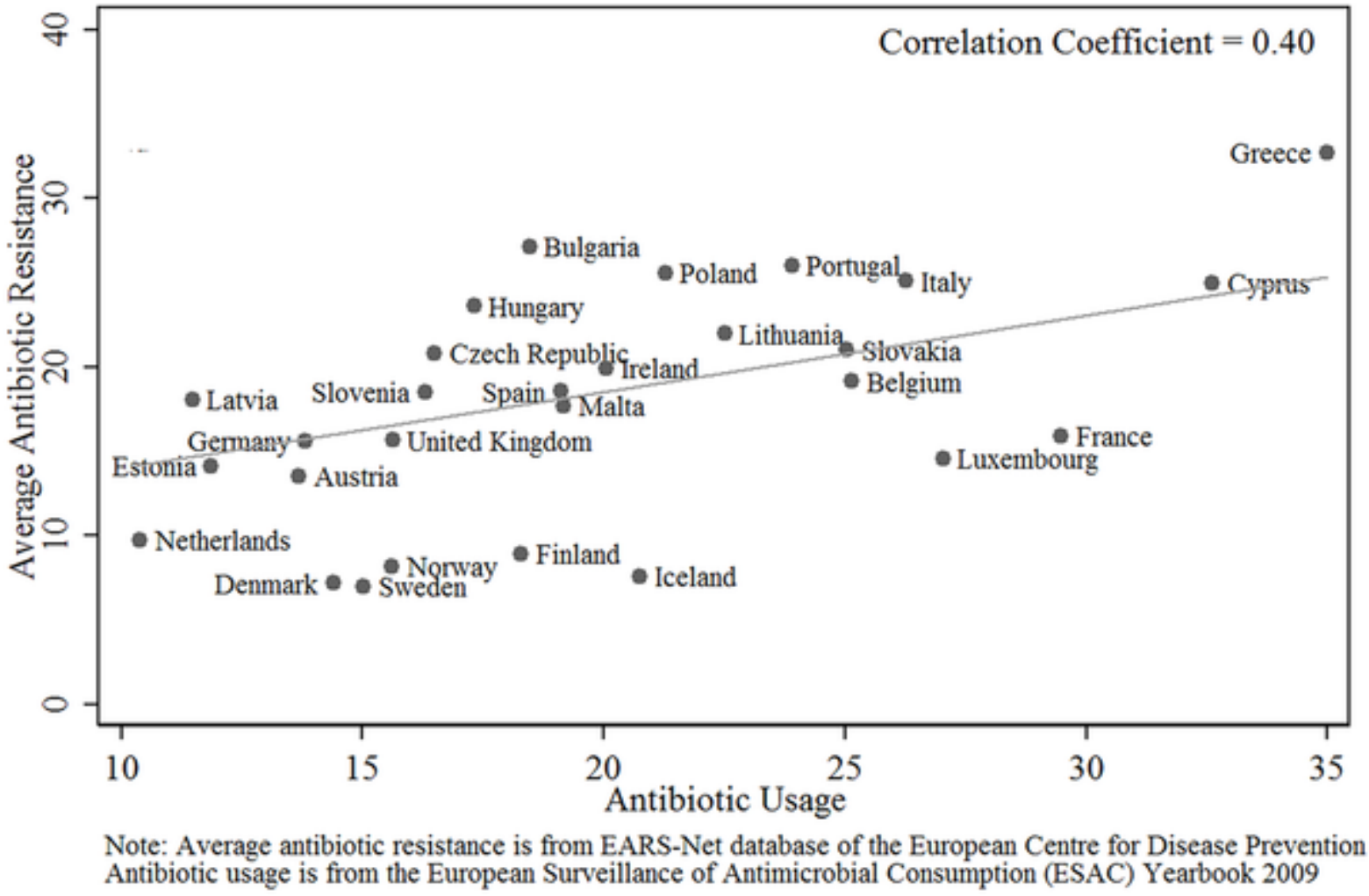
Fig 1. 'Average Microbial Resistance' against 'Antibiotic Use.'

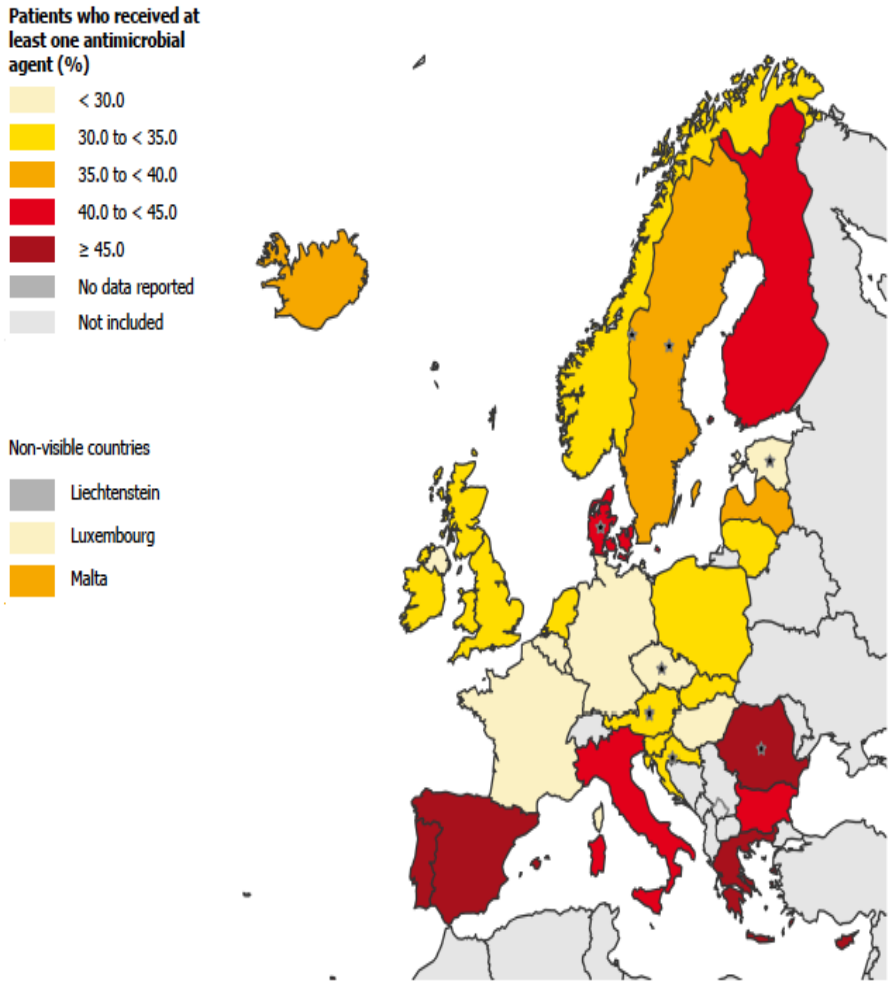


Note: Average antibiotic resistance is from EARS-Net database of the European Centre for Disease Prevention
Antibiotic usage is from the European Surveillance of Antimicrobial Consumption (ESAC) Yearbook 2009

Collignon P, Athukorala Pc, Senanayake S, Khan F (2015) Antimicrobial Resistance: The Major Contribution of Poor Governance and Corruption to This Growing Problem. PLoS ONE 10(3): e0116746. doi:10.1371/journal.pone.0116746
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0116746

Antimicrobial use in acute care hospitals in Europe

Prevalence of antimicrobial use in hospitals in acute care hospitals in Europe, ECDC PPS 2011-2012 in Europe



Percentage of antimicrobials for which the reason for use was documented in the patient's records in acute care hospitals in Europe, ECDC PPS 2011-2012 in Europe

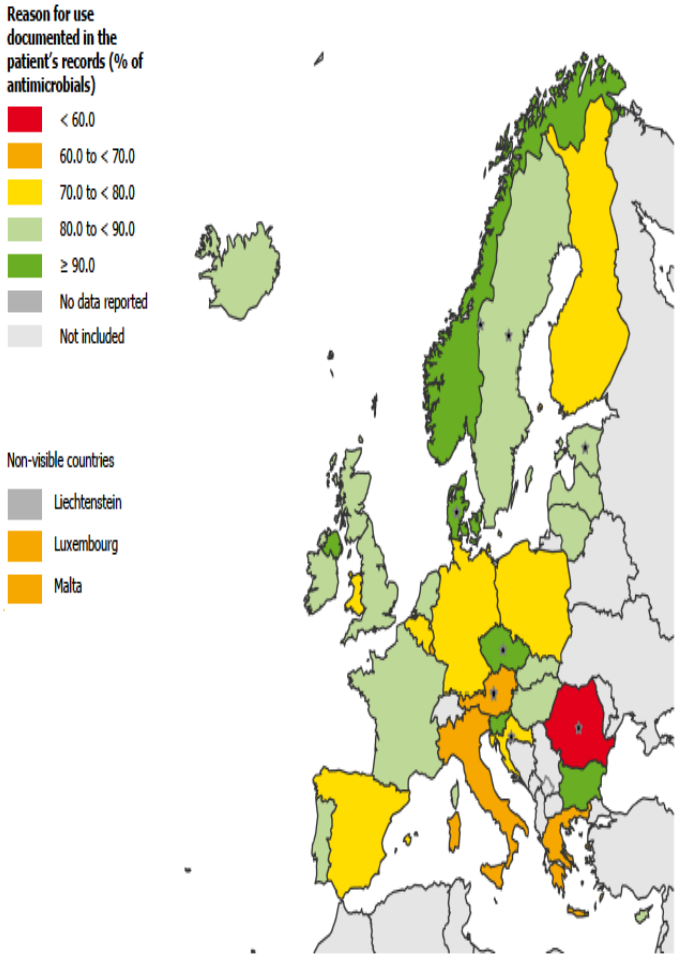
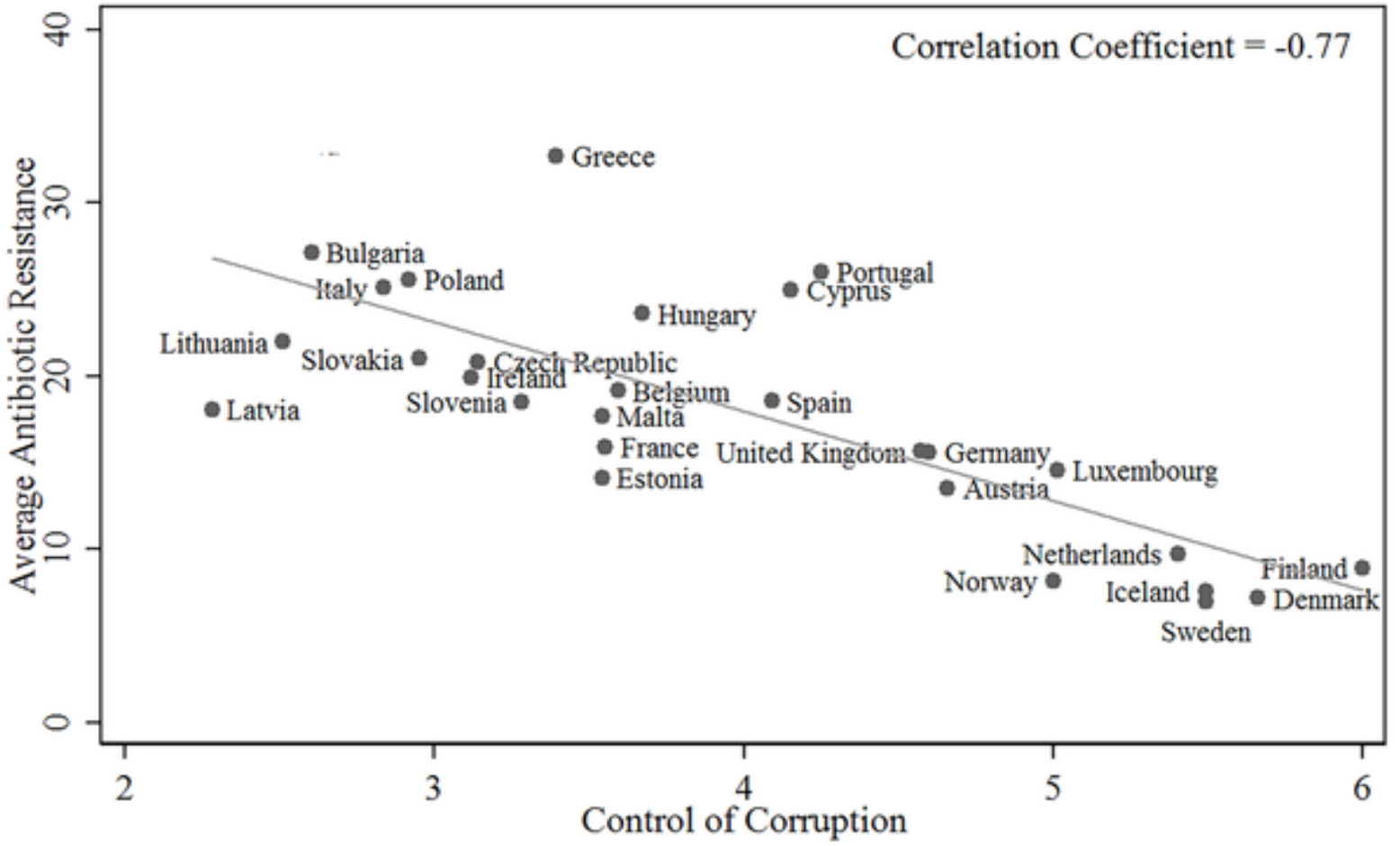


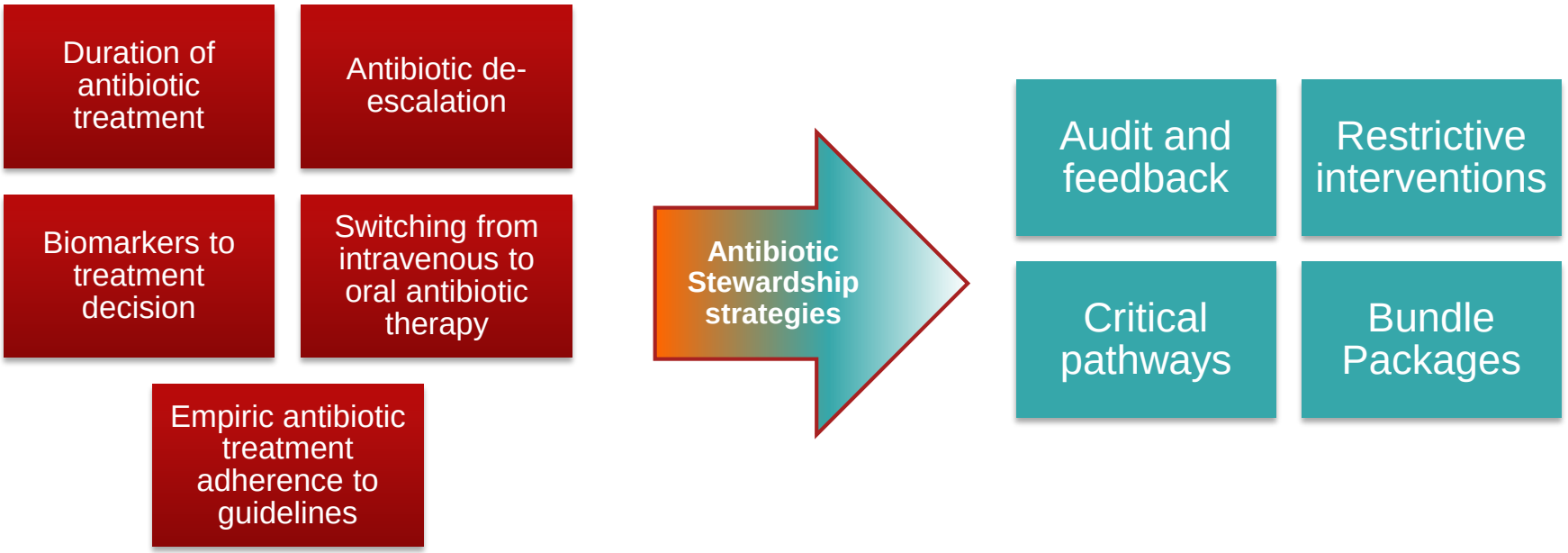
Fig 2. 'Average Microbial Resistance' against 'Control of Corruption.'



Note: Average antibiotic resistance is from EARS-Net database of the European Centre for Disease Prevention
The control of corruption indicator is from International Country Risk Guide

Collignon P, Athukorala Pc, Senanayake S, Khan F (2015) Antimicrobial Resistance: The Major Contribution of Poor Governance and Corruption to This Growing Problem. PLoS ONE 10(3): e0116746. doi:10.1371/journal.pone.0116746
http://journals.plos.org/plosone/article?id=info:doi/10.1371/journal.pone.0116746

Antimicrobial Stewardship in Pneumonia



The New Antibiotic Mantra—"Shorter Is Better"

Infections for which short antibiotic therapy has been shown to be equivalent to long term therapy

	Treatment, Days	
Disease	**Short**	**Long**
Community-acquired pneumonia[1-3]	3-5	7-10
Nosocomial pneumonia[6,7]	≤8	10-15
Pyelonephritis[10]	5-7	10-14
Intraabdominal infection[11]	4	10
Acute exacerbation of chronic bronchitis and COPD[12]	≤5	≥7
Acute bacterial sinusitis[13]	5	10
Cellulitis[14]	5-6	10
Chronic osteomyelitis[15]	42	84

Abbreviation: COPD, chronic obstructive pulmonary disease.

1. el Moussaoui BMJ. 2006; 332(7554):1355 2. Dunbar LM, Clin Infect Dis. 2003; 37(6):752–760. 3. Uranga A,. JAMA Internal Med..2016.3633. 6 Chastre J. JAMA. 2003; 290(19):2588–2598.7. Singh N. et al. Am J Respir Crit Care Med. 2000; 162(2, pt 1):505–511. 10. Eliakim-Raz N,et al . J Antimicrob Chemother. 2013; 68(10):2183–2191 11. Sawyer RG, N Engl J Med. 2015; 372(21):1996–2005 12. El Moussaoui R Thorax. 2008; 63(5):415–422 13. Falagas ME, Br J Clin Pharmacol. 2009; 67(2):161–17 14. Hepburn MJ,. Arch Intern Med. 2004; 164(15):1669–1674 15. Bernard LLanct. 2015; 385(9971):875–882. [PubMed: 25468170]

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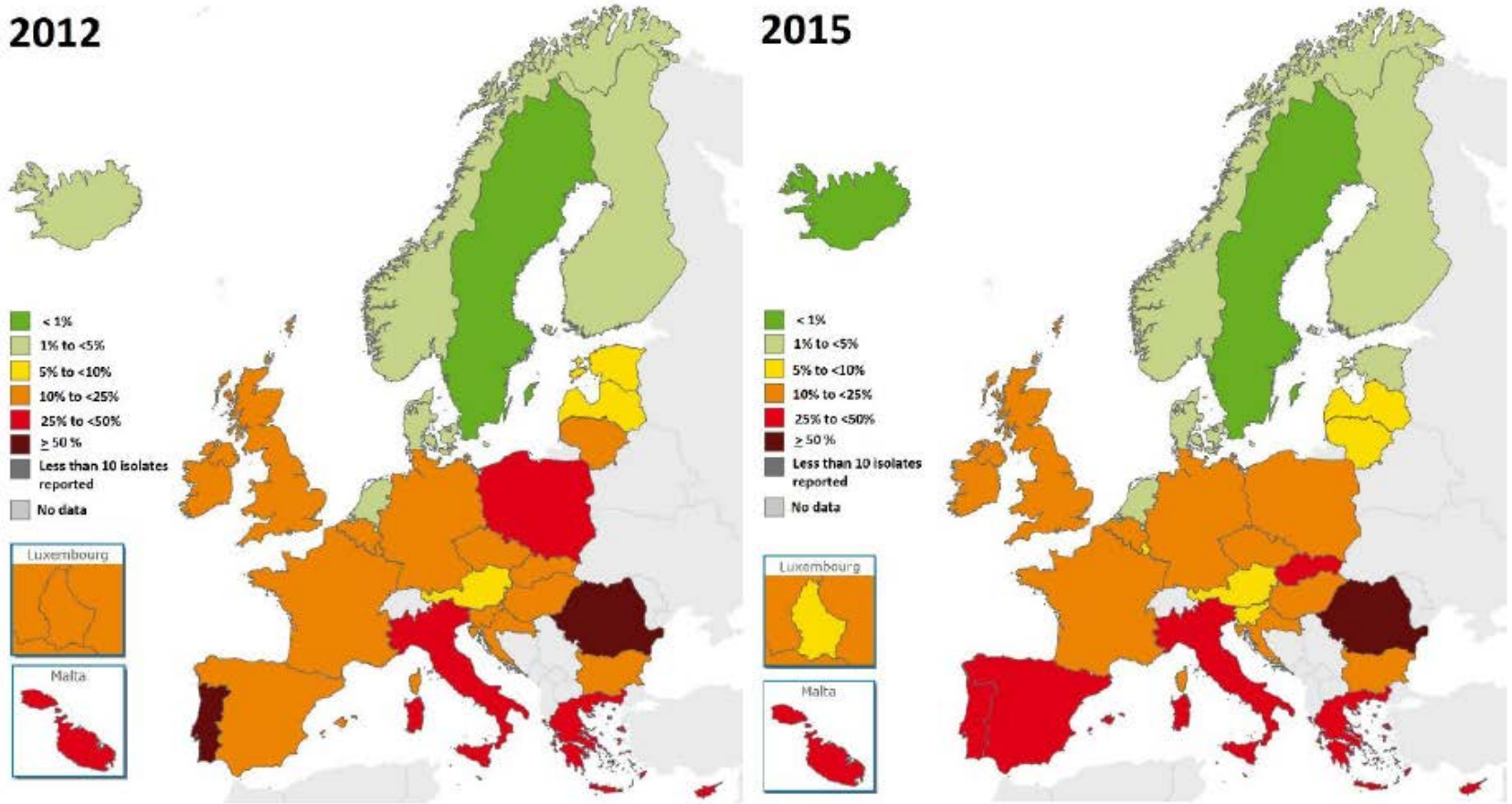
Surveillance of Antimicrobial Resistance

MRSA

Figure 7. ***Staphylococcus aureus*****: percentage of invasive isolates with resistance to meticillin (MRSA), EU/EEA, 2012 (left), 2015 (right)**



In Italy the proportion MRSA has decreased from 44.3% in 2012 to **34.1% in 2015**

Box 1: Drawbacks of the current therapeutic options for MRSA

Vancomycin

- Available for parenteral use only
- MIC creep
- Difficulties in attainment of therapeutic levels
- Emergence of VISA, hVISA, VRSA

Daptomycin

- Available for parenteral use only
- Not indicated for treatment of pneumonia

Linezolid

- Bacteriostatic
- Significant drug interactions
- Myelosuppressive

New anti gram-positives antibiotics

		cSSSi	CAP	HAP	VAP	notes
Ceftarolina Zinforo	Pfizer	X	X			No VAP 600 mg bid
Ceftobiprolo Mabelio	Cardiome Pharma		X	X		No VAP 500 mg tid
Telavancina * Vibativ	Astellas	X		X	X	Once-daily 10 mg/Kg No IR * When alternative treatment is not suitable
Dalbavancin Xydalba	Angelini	X				IV single dose 1500mg
Oritavancin Orbactiv	The Medicines Company	X				IV Single dose 1200 mg
Tedizolid Sivextro	MSD	X	Registration ongoing			200 mg IV/OS X 6 days

Advanced cephalosporins: Ceftaroline

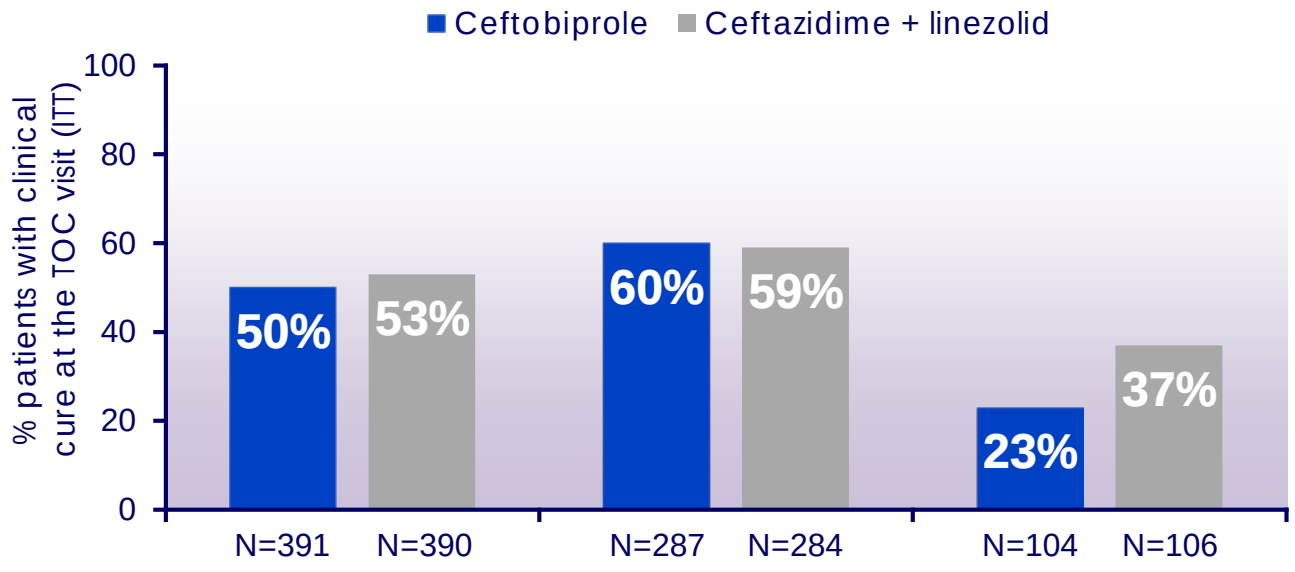
- Parenteral, bactericidal, anti-MRSA cephalosporin
- Activity vs. Gram-pos. and neg. bacteria in cSSTI
  - No activity against ESBLs and *P. aeruginosa*
- Bactericidal; IV 600 mg b.i.d.
- EU approval (August 2012) for:

1. cSSTI
2. CAP in adults

Advanced Cephalosporins: Ceftobiprole

- **Enhanced gram-pos. spectrum: MRSA, VISA, EF, PRP**
- **Enterobacteriaceae activity (no ESBL & no AmpC)**
- ***P.aeruginosa* activity (=cefepime)**
- **MIC range 0.5 – 2 mg/L**
- **Bactericidal; IV 500 mg t.i.d.**
- **$t_{1/2}$ = 3 – 4 h**
- **Elimination: renal**

Ceftobiprole vs Ceftazidime linezolid in HAP
Primary Endpoint: Clinical cure at TOC



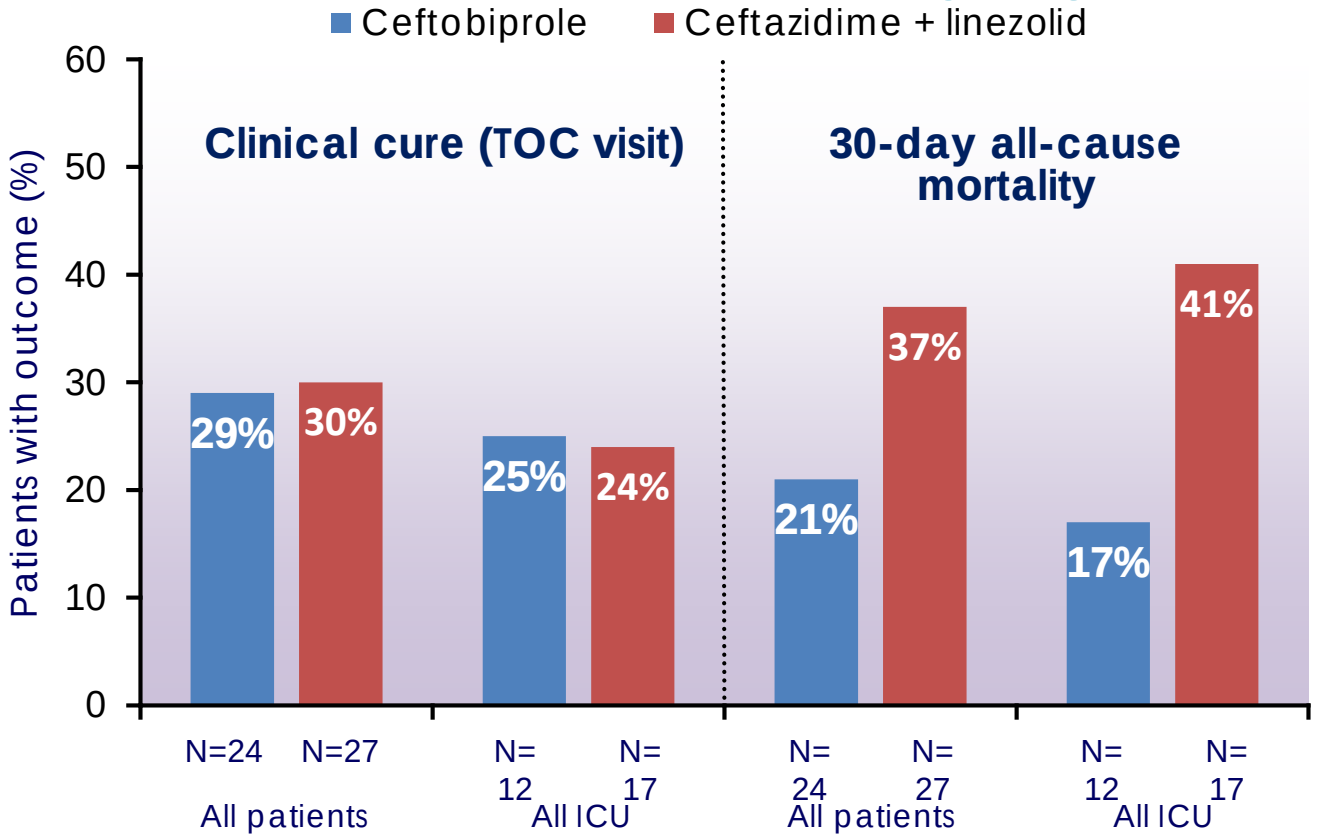
Ceftobiprole *vs* ceftazidime + linezolid	All patients	HAP (excl. VAP)	VAP
~~Difference~~ (95% CI):	**-2.9%** (-10.0; 4.1)	**0.8%** (-7.3; 8.8)	**-13.7%** (-26.0; -1.5)

Ceftobiprole not inferior to ceftazidime/linezolid in all patients and HAP (exl. VAP) patients in IIT-group

HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia
ITT, intent-to-treat; TOC, test of cure (7–14 days after end of treatment)

Awad SS, et al. Clin Infect Dis 2014; 59:51-61.

HAP (excl. VAP): Outcomes in patients with baseline bacteremia (ITT)



HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia
ICU, intensive care unit; ITT, intent-to-treat; TOC, test of cure test of cure (7–14 days after end of treatment)

Welte T, et al. Presentation at ERS 2014; Presentation 4643.

Ceftobiprole medocaril in patients with hospital-acquired pneumonia (HAP) or community-acquired pneumonia (CAP): a summary
Intravenously administered new generation broad-spectrum cephalosporin, with activity against methicillin-resistant *Staphylococcus aureus* (MRSA)
First anti-MRSA cephalosporin monotherapy to be approved in the EU for both HAP (excluding ventilator-associated pneumonia) and CAP
Noninferior to ceftazidime plus linezolid in patients with HAP (excluding patients with ventilator-associated pneumonia) and ceftriaxone ± linezolid in those with CAP
Generally well tolerated
Offers simplified monotherapy option relative to combination therapies for initial empirical treatment

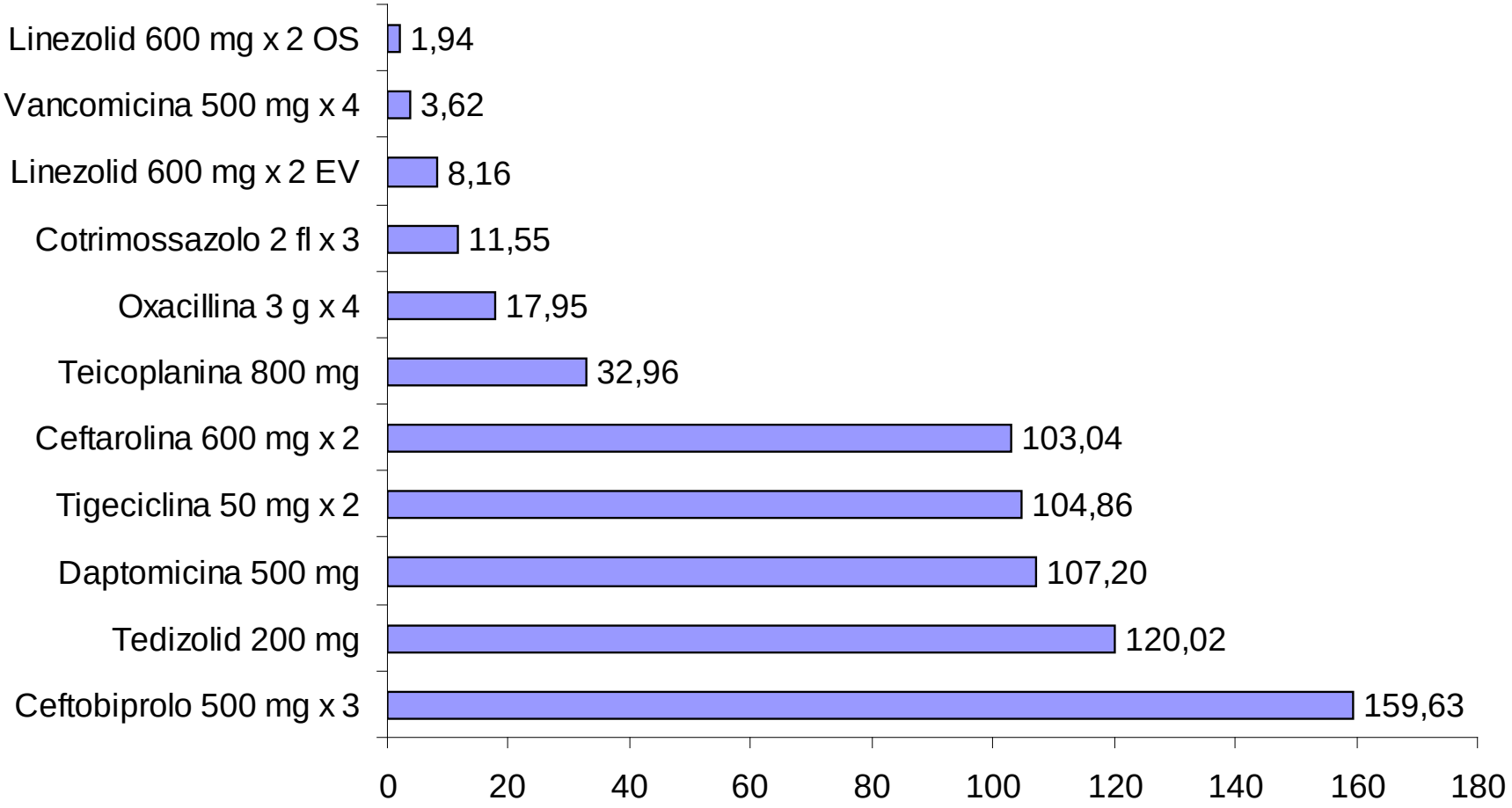
Tedizolid

- **Highly active against *S. aureus* (MSSA, MRSA), *Str. pyogenes*, *Str. agalactiae*, the *Str. anginosus* group, and *E. faecalis*, including those with some mechanism of resistance limiting the use of linezolid.**
- **The AUC/MIC PD ratio has shown the best correlation with the efficacy**

Benefits and disadvantages compared to other oxazolidinone antibiotics

- **Higher activity against Gram-positive microorganisms**
- **Bioavailability high and similar to linezolid.**
- **More favorable PK, prolonged half-life, single daily dose.**
- **Lower risk of hematological AEs & serotonin syndrome**
- **Tedizolid 6 days not inferior to linezolid 10 days.**
- **Short treatment currently evaluated in pneumonia.**
- **Tedizolid could be associated with reduced economic resources mainly deriving from a shorter LOS**

ANTIBATTERICI VS GRAM POSITIVI
Costo terapia giornaliera (€)



Costo 1 ciclo (15 GIORNI) Dalbavancina (1.500 mg) = € 1.276,24

Newer antibiotics active against MRSA

Drug	Indications	Advantages	Drawbacks	Comments
Newer fluoroquinolones (avarofloxacin, delafloxacin, finafloxacin, nemonoxacin zabofloxacin)	*ABSSSI, CAP, sexually transmitted infections*	Broad spectrum, activity in acidic pH	Some agents exhibit higher MIC for quinolone resistant isolates	Currently undergoing evaluation in clinical trials
Lefamulin	*ABSSSI, CAP*	Broad Gram-positive spectrum and fastidious Gram-negative bacteria	Does not cover *E. faecalis*, susceptible to *cfr* gene mediated resistance	Currently undergoing evaluation in clinical trials

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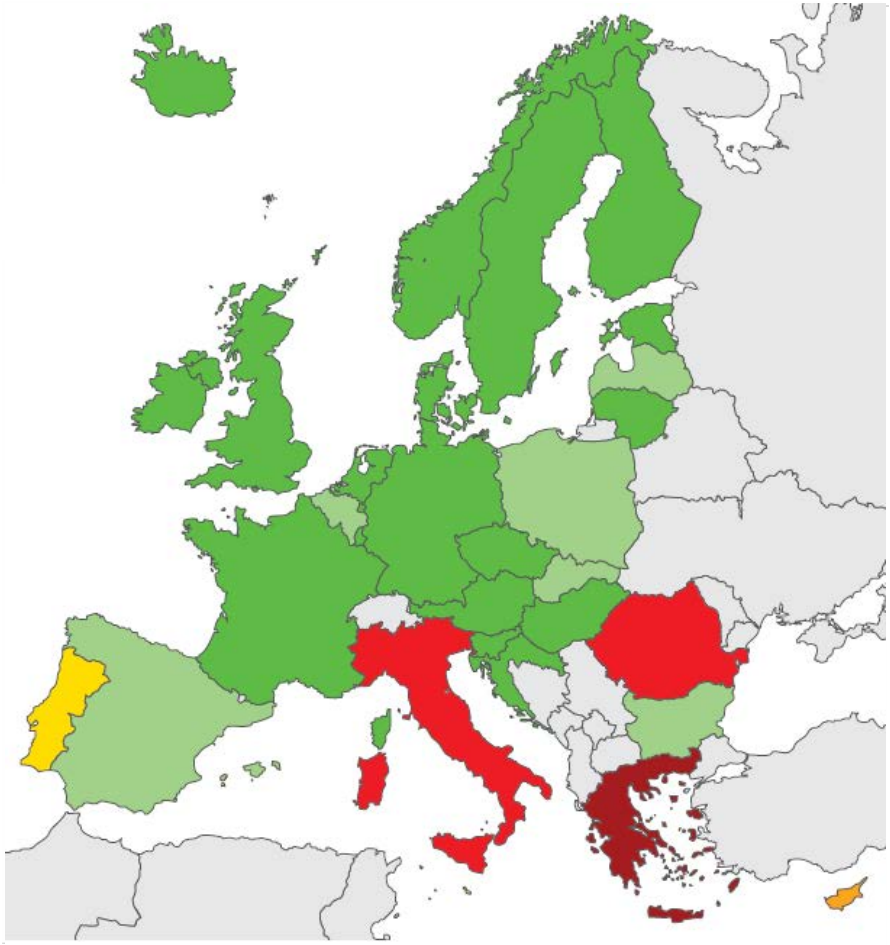
Klebsiella pneumoniae: percentage of invasive isolates with resistance to carbapenems



- < 1%
- 1% to < 5%
- 5% to < 10%
- 10% to < 25%
- 25% to < 50%
- ≥ 50%
- No data reported or less than 10 isolates
- Not included

2009 → 2016

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

The complex world of beta-lactamases

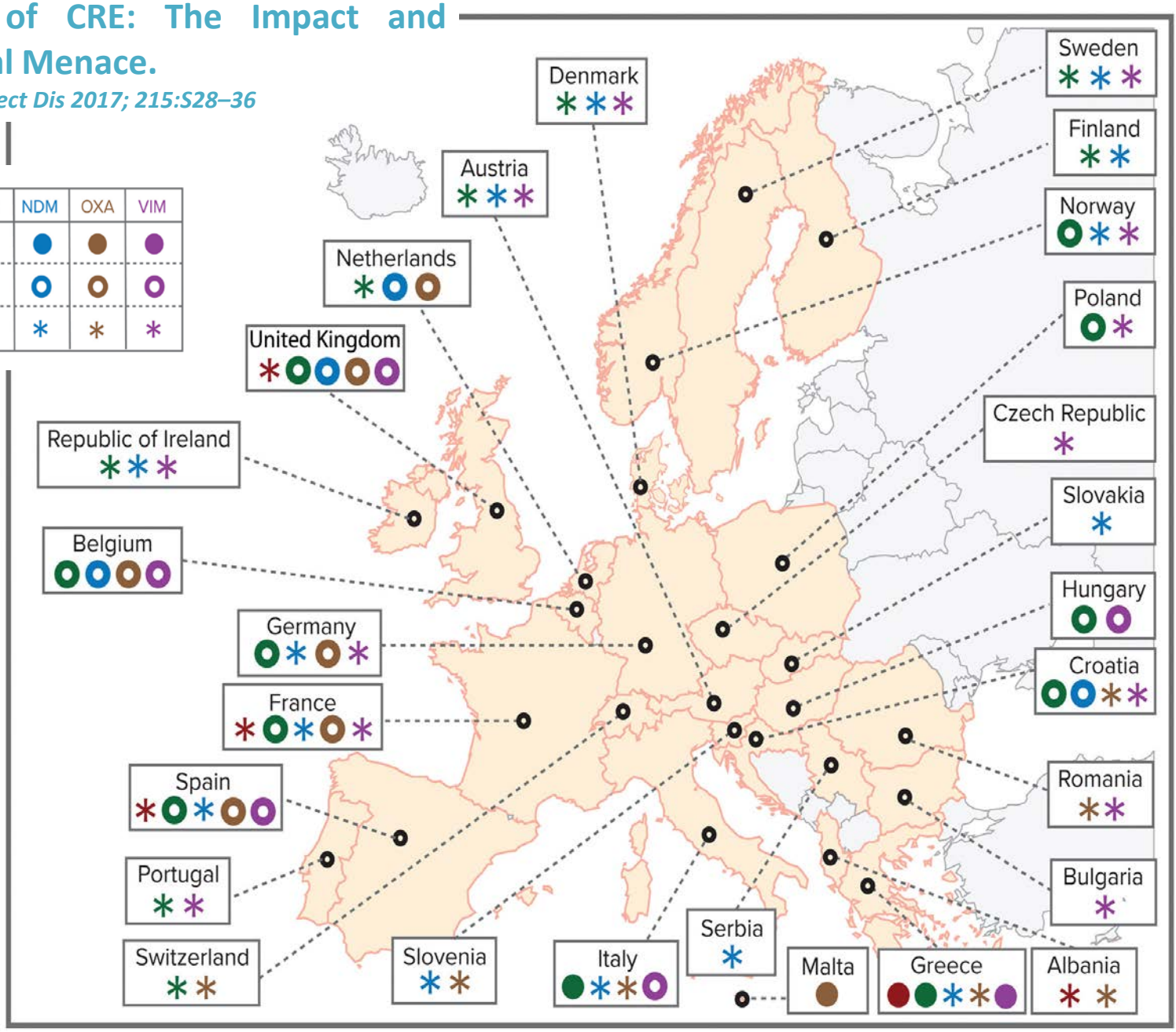
	C	A	A	A	A	D	B
	β-lactamase enzyme						
	AmpC	CTX-M	SHV	TEM	KPC	OXA-48	MBL
Sulbactam	-/+	+	-	-	-	-	-
Clavulanic acid	-	+	-	-	-	-	-
Tazobactam	-	+	-	-	-	-	-
Avibactam	+	+	+	+	+	+	-
Monobactams	-	-	-	-	-	-	+
Carbapenems	+	+	+	+	-	-	-

*TEM-30 and SHV-10 (Subgroup 2br) and TEM -50 (Subgroup 2ber) are resistant to clavulanic acid, tazobactam and sulbactam

The Epidemiology of CRE: The Impact and Evolution of a Global Menace.

Logan LK & Weinstein RA J Infect Dis 2017; 215:S28–36

	IMP	KPC	NDM	OXA	VIM
Endemic/nationwide distribution	●	●	●	●	●
Significant outbreaks/ regional spread	○	○	○	○	○
Sporadic outbreak/ occurences	*	*	*	*	*



Carbapenem Resistant Enterobacteriaceae

Carbapenem-resistant *Enterobacteriaceae* encompass both carbapenemase-producing and non-CP types.

non-CP-CRE ← heterogeneous mechanisms,, →loss of organism fitness and reduced transmissibility

CP-CRE → mobile genetic elements easily transmissible to other Gram negative organisms.

MOLECULAR RAPID MICROBIOLOGY IS MANDATORY !

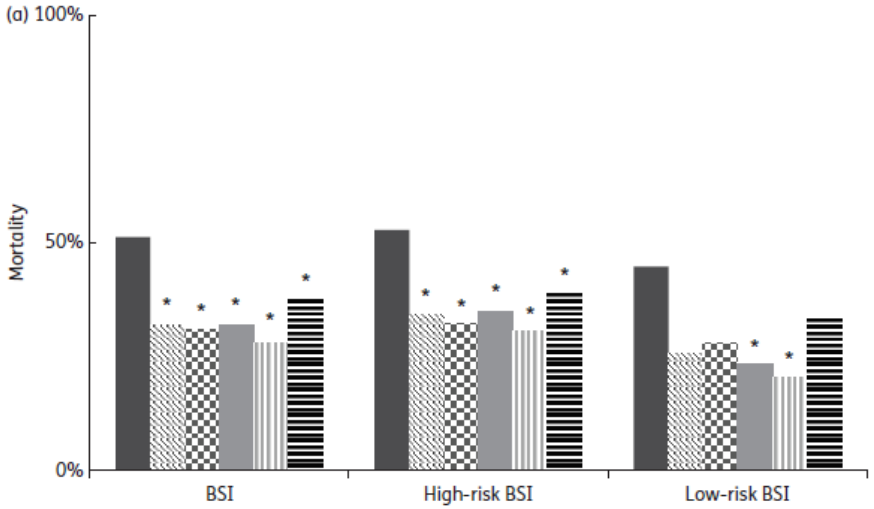
2015

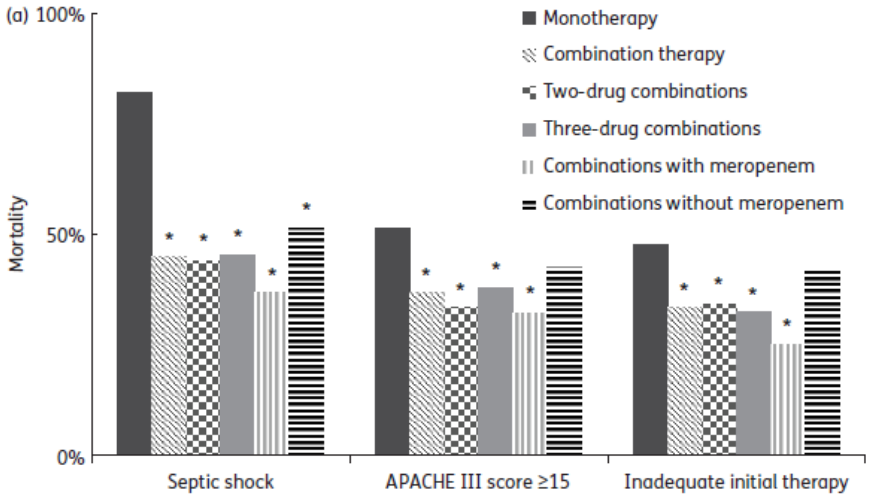
J Antimicrob Chemother
doi:10.1093/jac/dkv086

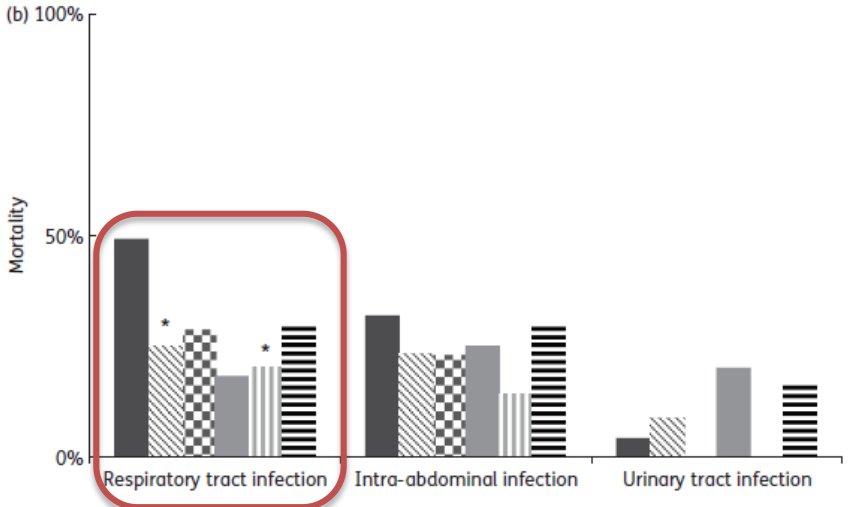
Journal of Antimicrobial Chemotherapy

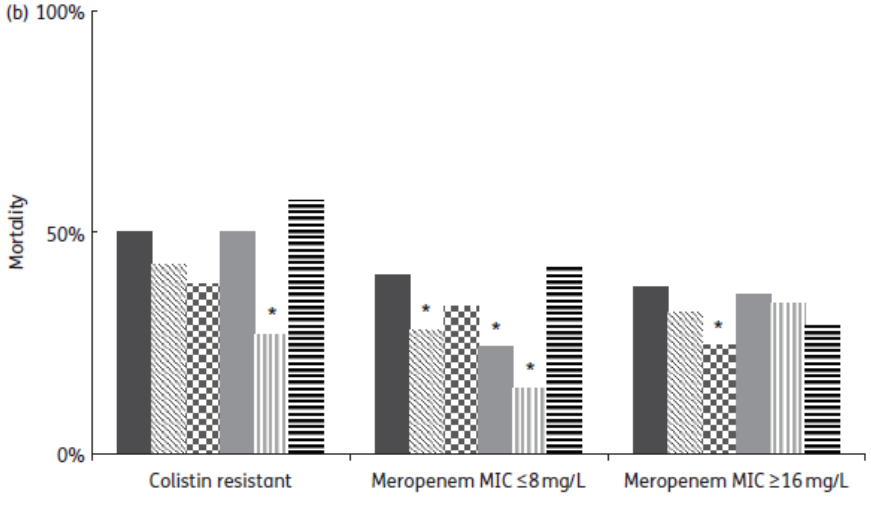
Infections caused by KPC-producing *Klebsiella pneumoniae*: differences in therapy and mortality in a multicentre study

Mario Tumbarello[1]*, Enrico Maria Trecarichi[1], Francesco Giuseppe De Rosa[2,3], Maddalena Giannella[4], Daniele Roberto Giacobbe[5], Matteo Bassetti[6], Angela Raffaella Losito[1], Michele Bartoletti[4], Valerio Del Bono[5], Silvia Corcione[2,3], Giuseppe Maiuro[1], Sara Tedeschi[4], Luigi Celani[1], Chiara Simona Cardellino[2,3], Teresa Spanu[7], Anna Marchese[8], Simone Ambretti[9], Roberto Cauda[1], Claudio Viscoli[5] and Pierluigi Viale[4] on behalf of ISGRI-SITA (Italian Study Group on Resistant Infections of the Società Italiana Terapia Antinfettiva)





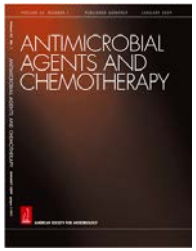




Strategy For Treating CRE severe infections

1. Use standard antibiotics **at doses that result in higher PK exposure**, so PK:PD targets are still achieved
2. Use **non-standard / new antibiotics for which resistance has not yet occurred**
3. **Use combination therapy** with antibiotics from option #1 and option #2

Carbapenemase-Producing *Klebsiella pneumoniae* Bloodstream Infections: Lowering Mortality by Antibiotic Combination Schemes and the Role of Carbapenems



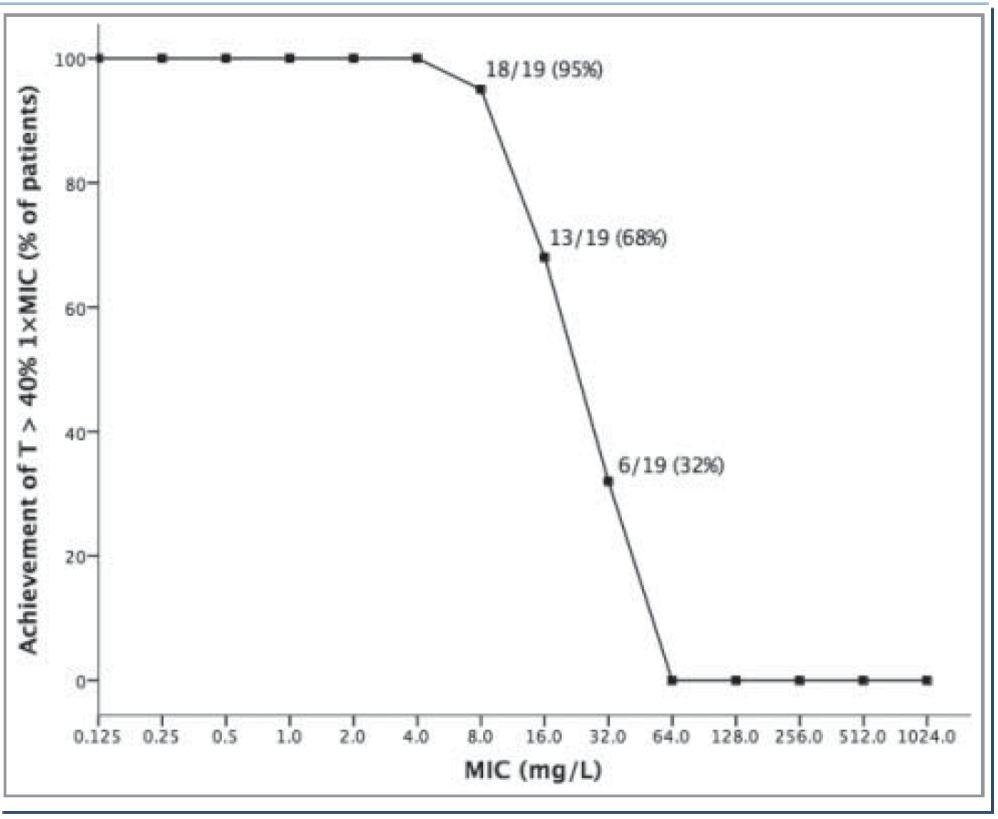
2014

George L. Daikos,[a] Sophia Tsaousi,[b] Leonidas S. Tzouvelekis,[c] Ioannis Anyfantis,[a] Mina Psichogiou,[a] Athina Argyropoulou,[d] Ioanna Stefanou,[e] Vana Sypsa,[f] Vivi Miriagou,[g] Martha Nepka,[d] Sarah Georgiadou,[a] Antonis Markogiannakis,[h] Dimitris Goukos,[a] Athanasios Skoutelis[b]

TABLE 4 Outcomes of 79 patients with CP-Kp bloodstream infections treated with carbapenem combinations stratified by carbapenem MIC

	Result for carbapenem combination with:			
	In vitro active agent(s)		*In vitro* inactive agent(s)	
Carbapenem MIC (μg/ml)	No. of patients who survived/died	Mortality, %	No. of patients who survived/died	Mortality, %
≤8	25/6	19.3	5/7	58.3
>8	20/11	35.5	4/2	33.3

19 critically-ill patients with BSI due to KPC-Kp with MEM MICs ≥ 16 mg/L were given combination therapy including MEM, tigecycline, plus colistin or gentamicin



High-dose MEM failed to reach PK/PD targets in patients with BSI due to KPC-Kp with very high MEM MICs.

On a theoretical basis, our results suggest a possible usefulness of MEM against resistant blood isolates with MICs up to 32 mg/L.

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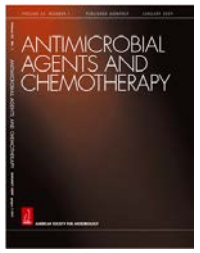
LETTER TO THE EDITOR



Successful Ertapenem-Doripenem Combination Treatment of Bacteremic Ventilator-Associated Pneumonia Due to Colistin-Resistant KPC-Producing *Klebsiella pneumoniae*

Giancarlo Ceccarelli,[a] Marco Falcone,[b] Alessandra Giordano,[a] Maria Lina Mezzatesta,[c] Carla Caio,[c] Stefania Stefani,[c] Mario Venditti[a]

2013

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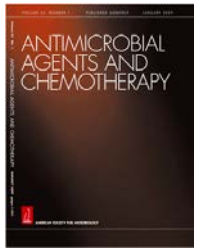
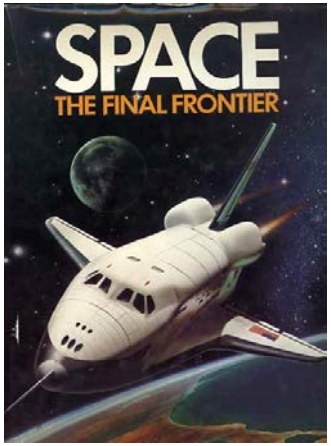


Effectiveness of a Double-Carbapenem Regimen for Infections in Humans Due to Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae*

Helen Giamarellou, Lambrini Galani, Fotini Baziaka, Ilias Karaiskos

6th Department of Internal Medicine, Hygeia General Hospital, Athens, Greece



2014

J Antimicrob Chemother
doi:10.1093/jac/dku027

Synergistic activity and effectiveness of a double-carbapenem regimen in pandrug-resistant *Klebsiella pneumoniae* bloodstream infections

Alessandra Oliva[1]†, Alessandra D'Abramo[1]†, Claudia D'Agostino[1], Marco Iannetta[1], Maria T. Mascellino[1], Carmela Gallinelli[1], Claudio M. Mastroianni[1,2]* and Vincenzo Vullo[1]

Re-emerging agents in the treatment of infections caused by CRE

drug	Class	Pitfalls / peculiarities
FOSFOMYCIN	**Phosponic acid**	**R during treatment**
TYGECYCLINE	**glycilcline**	**In vitro chemoS / daily dose**
MINOCYCLINE	**tetracycline**	**Low Sensitivity rates for KPC**
CO-TRIMOXAZOLE	**Anti folic**	**Scanty clinical informations**

RE-Emerging agents against CRE – UNMET NEEDS

Addition of carbapenems is not useless → but until certain levels of MIC (< 64)

→ the «MIC creep» of carbapenems

Use of double carbapenem therapy ?

Colistin in respiratory tract infection → aerosol supplement How? How Long?

Colistin resistance

Tygeciclin → increasing dose is enough

Low reliability of standard chemosensitivity tests

Newer agents in the treatment of infections caused by CRE

drug	Class	Pitfalls / peculiarities
CEFTAZIDIME-AVIBACTAM	BL/BLI	No activity against MBL
AZTREONAM-AVIBACTAM	BL/BLI	selective vs B b-lactamese
MEROPENEM-VABORBACTAM	BL/BLI	Selective vs A & C b-lactamase
IMIPENEM-RELEBACTAM	BL/BLI	Selective vs A & C b-lactamase
PLAZOMYCIN	Aminoglyxoside	Toxicity?
EVERACYCLINE	Florocycline	2 -4 fold more potent than Tyge

CEFTAZIDIME-AVIBACTAM

Avibactam is a non–b-lactam b-lactamase inhibitor, acting against the activities of Ambler class A and C and some Ambler class D enzymes

•Through the addition of avibactam, ceftazidime's activity is expanded to many ceftazidime-resistant and carbapenem-resistant Enterobacteriaceae and P. aeruginosa. This includes isolates producing a variety of Ambler class A and C b-lactamases including AmpC, ESBLs, and KPC, as well as select class D OXA enzymes.

•In contrast, ceftazidime-avibactam does not possess any appreciable activity against the Ambler class B metallo–b-lactamases.

•FDA approved as rescue option for CIAI and cUTI

Colistin vs. Ceftazidime-avibactam in the Treatment of Infections due to CRE

van Duin D et al, J Antimicrob Chemother 2017 , in press

Patients initially treated with either ceftazidime-avibactam or colistin for CRE infections were selected from the Consortium on resistance against carbapenems in *Klebsiella* and other Enterobacteriaceae (CRACKLE), a prospective, multicenter, observational study. Thirty-eight patients were treated first with ceftazidime-avibactam and 99 with colistin were evaluated

Efficacy: disposition	CAZ-AVI N = 38	COLISTIN N = 99	Δ (95% CI)
Hospital death	9%	32%	23% (9, 35)
Not died with ARF	5%	13%	24% (4, 43)

Clinical outcomes, drug toxicity and emergence of ceftazidime-avibactam Resistance among patients treated for carbapenem-resistant Enterobacteriaceae infections

Shields RK et al Clin Infect Dis 2016 Sep 16

Thirty-seven carbapenem-resistant Enterobacteriaceae-infected patients were treated with ceftazidime-avibactam. It was administered as monotherapy or in combination regimens in 70% (26/37) and 30% (11/37) respectively

Infections included pneumonia (n=12) primary bacteremia (n=10), intra-abdominal infection (n=4), skin/soft tissue infection (n=4), pyelonephritis (n=4) and mediastinitis, subdural empyema, and purulent tracheobronchitis (1 each).

Clinical success and survival rates at 30-days were 59% (22/37) in monotherapy and 76% (28/37)in combination therapy, respectively.

In 23% (5/22) of clinical successes, CRE infections recurred within 90-days. Microbiologic failure rate was 27% (10/37).

Ceftazidime-avibactam resistance was detected in 30% (3/10) of microbiologic failures.

Emergence of Ceftazidime-Avibactam Resistance and Restoration of Carbapenem Susceptibility in Klebsiella pneumoniae CarbapenemaseProducing K pneumoniae: A Case Report and Review of Literature Ryan K. Shields

			MIC (μg/mL)[b]			Log-Kill at 24 Hours in Presence of Meropenem[c]		
Isolate	ST	KPC Variant	Ceftazidime-Avibactam	Ceftazidime	Meropenem	4× MIC	8× MIC	16 μg/mL
1-A	**258**	**KPC-3**	**2 (S)**	**512**	**128**	[d]	[d]	**+3.53**
1-B	258	D179Y, T243M	256	>512	0.5 (S)	−4.97	−4.27	−4.97
1-C	258	D179Y, T243M	256	>512	0.25 (S)	−5.94	−4.94	−5.96
2-A	**258**	**KPC-3**	**4 (S)**	**256**	**32**	[d]	[d]	**+3.57**
2-B	258	V240G	32	>512	8	−6.14	−6.14	−6.14
2-C	258	D179Y	>256	>512	4	−4.64	−5.64	−4.64
3-A	**258**	**KPC-3**	**2 (S)**	**256**	**32**	[d]	[d]	**+3.52**
3-B	258	D179Y	128	512	0.25 (S)	−5.98	−5.98	−5.98
3-C	258	D179Y	64	512	0.125 (S)	−3.18	−3.18	−5.83
4-A	**258**	**KPC-3**	**1 (S)**	**256**	**16**	[d]	[d]	**+3.52**
4-B	258	A177E, D179Y	256	256	0.25 (S)	−3.70	−5.16	−6.16
4-C	258	A177E, D179Y	128	256	0.25 (S)	−3.26	−2.54	−5.96

Ceftazidime-avibactam resistance has emerged in ~10% of CR-Kp-infected patients treated at our center [2, 4]. Thus far, these are the only cases reported to develop during treatment. Resistance has been diagnosed after 10–19 days of drug exposure, exclusively in KPC-3-producing ST258 isolates. It is conferred by **plasmid-borne blaKPC-3 muta**tions, which **reduce MICs of carbapenems** (often restoring susceptibility) and other β-lactams

Synergistic activity of ceftazidime-avibactam and aztreonam against serine and metallo-β-lactamase-producing gram-negative pathogens
Wenzler E et al, Diagnostic Microbiol Infect Dis 2017;88: 352–354

Organism	MIC (μg/mL)		
	Ceftazidime	Aztreonam	Ceftazidime-avibactam
E. coli NDM	>256	>256	>256/4
P. aeruginosa IMP	>256	32	>256/4
C. freundii VIM	>256	8	>256/4
E. cloacae KPC	>256	>256	2/4
K. pneumoniae KPC	>256	>256	2/4
A. baumannii OXA	>256	32	16/4
K. pneumoniae ATCC[a]	32	>256	2/4

Organism	Ceftazidime + Aztreonam		Ceftazidime + Ceftazidime-avibactam		Aztreonam + Ceftazidime-avibactam	
	∑FIC	Interpretation	∑FIC	Interpretation	∑FIC	Interpretation
E. coli NDM	2	I	2	I	0.016	S
P. aeruginosa IMP	0.5	S	2	I	1.5	I
C. freundii VIM	0.5	S	2	I	0.031	S
E. cloacae KPC	0.125	S	0.011	S	0.009	S
K. pneumoniae KPC	0.125	S	0.039	S	0.011	S
A. baumannii OXA	0.094	S	0.063	S	1	A
K. pneumoniae ATCC	0.25	S	0.078	S	0.0094	S

CEFTAZIDIME AVIBACTAM – open questions

ALONE or INSIDE COMBO REGIMENS ?

IF COMBO, WHICH PARTNER/s ? carbapemens, aminoglycosides, fosfomycin ?

FIRST LINE OR RESCUE OPTION ?

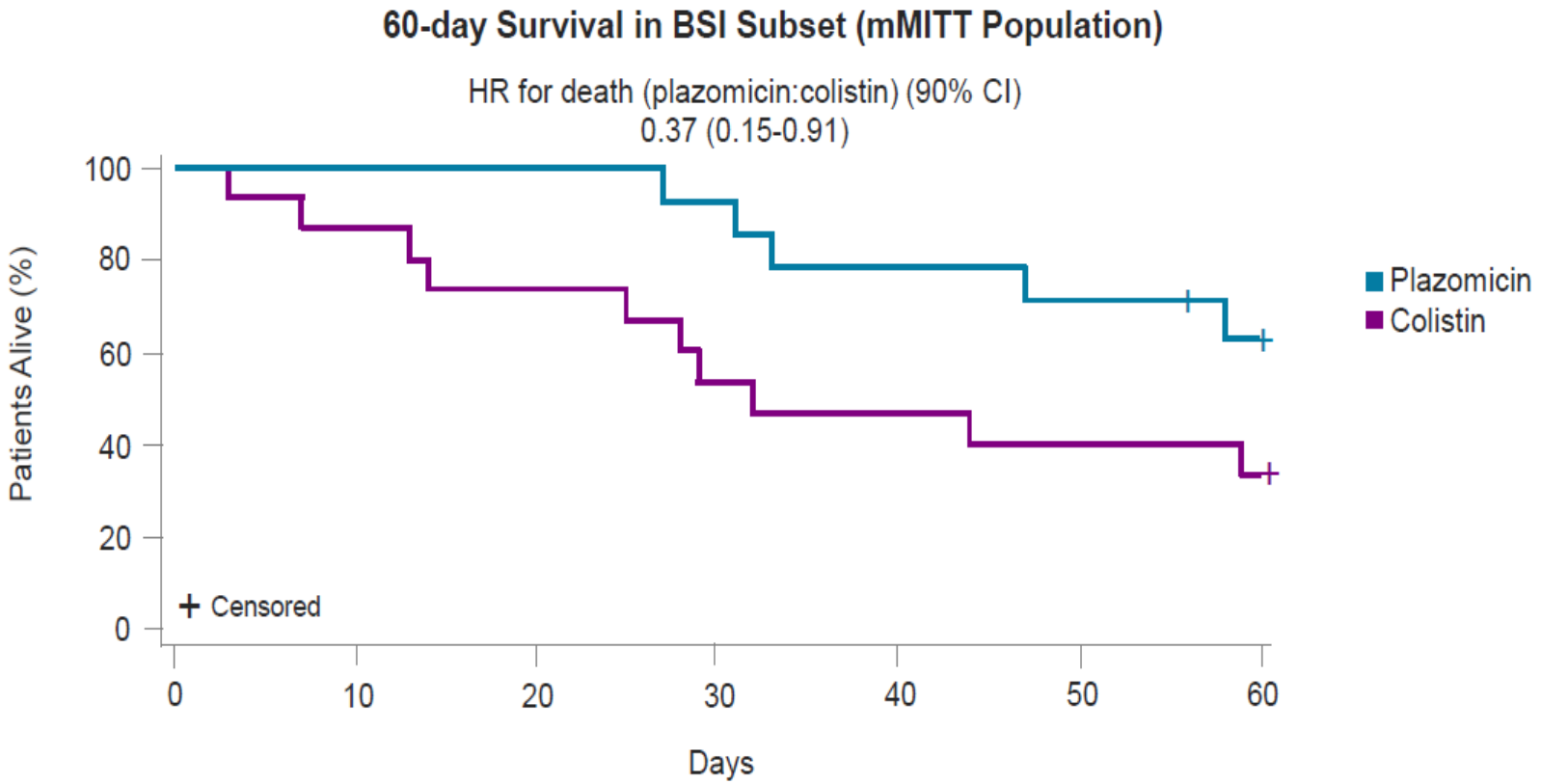
A DAILY DOSE OVER THE LABEL ?

Plazomicin (ACHN-490, Achaogen)

- Aminoglycoside, IV only
  - A chemical modificaion of sisomicin
- Gram-negative spectrum
  - Bactericidal
- Phase 3 clinical trial to evaluate efficacy and safety of plazomicin compared with colistin for infections caused by Carba Res Enterobact.
- Phase 3 vs. colistin for the treatment of patients with bloodstream infection (BSI) or nosocomial pneumonia due to CRE

www.clinicaltrials.gov; www.achaogen.com

CARE Kaplan-Meier Survival Curve
Sustained Survival Benefit in Plazomicin-treated Patients With BSI



Estimate of hazard ratio (HR) calculated as plazomicin:colistin based on Cox proportional hazards regression model.

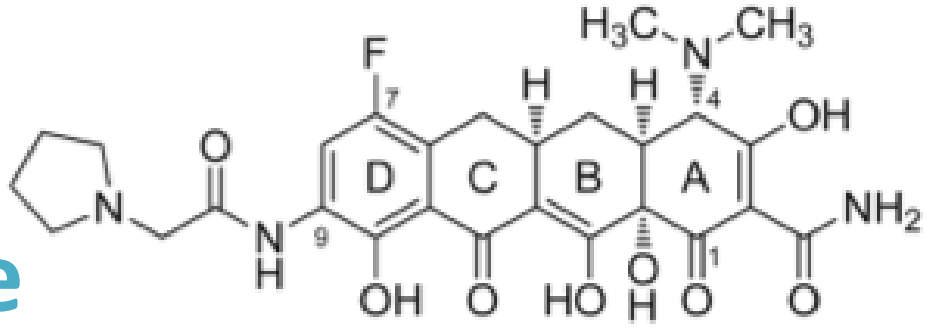
Imipenem/relebactam

Relebactam is a novel beta-lactamase inhibitor active against AmpC, ESBLs and KPC

Active against *Pseudomonas aeruginosa* isolates with OprD mutations leading to imipenem resistance

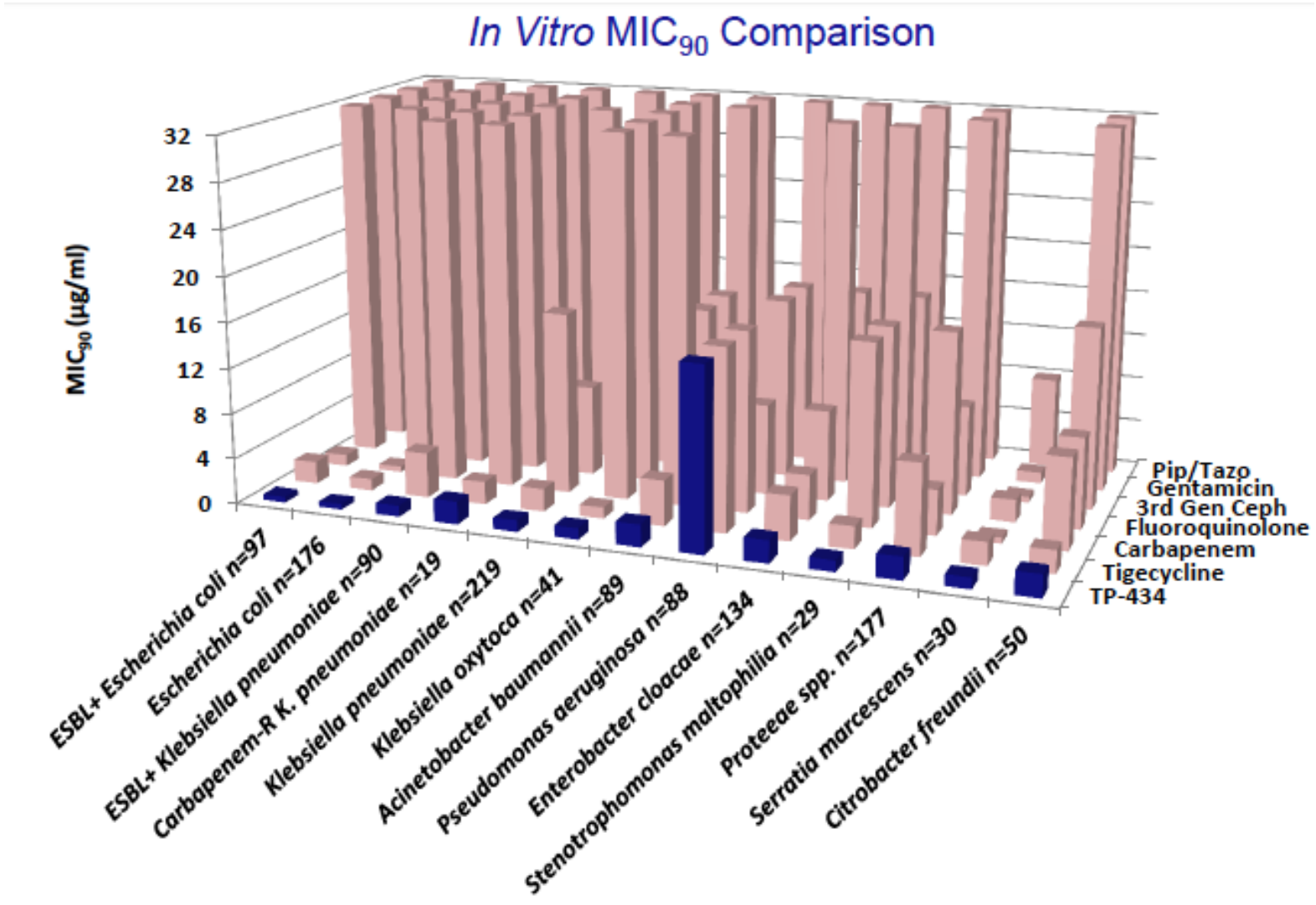
No activity against MBLs

Eravacycline: A Fluorotetracycline



- Fully synthetic fluorocycline with broad spectrum activity including MDR Gram-positive, Gram-negative, and anaerobic organisms (excepting *Pseudomonas*)
- Highly active against Enterobacteriaceae harboring ESBLs and carbapenemases
- Activity against isolates containing tetracycline-specific efflux and ribosomal protection mechanisms
- High bioavailability in oral formulations
- Effective in cUTIs and in cIAI (Phase 2 and 3)

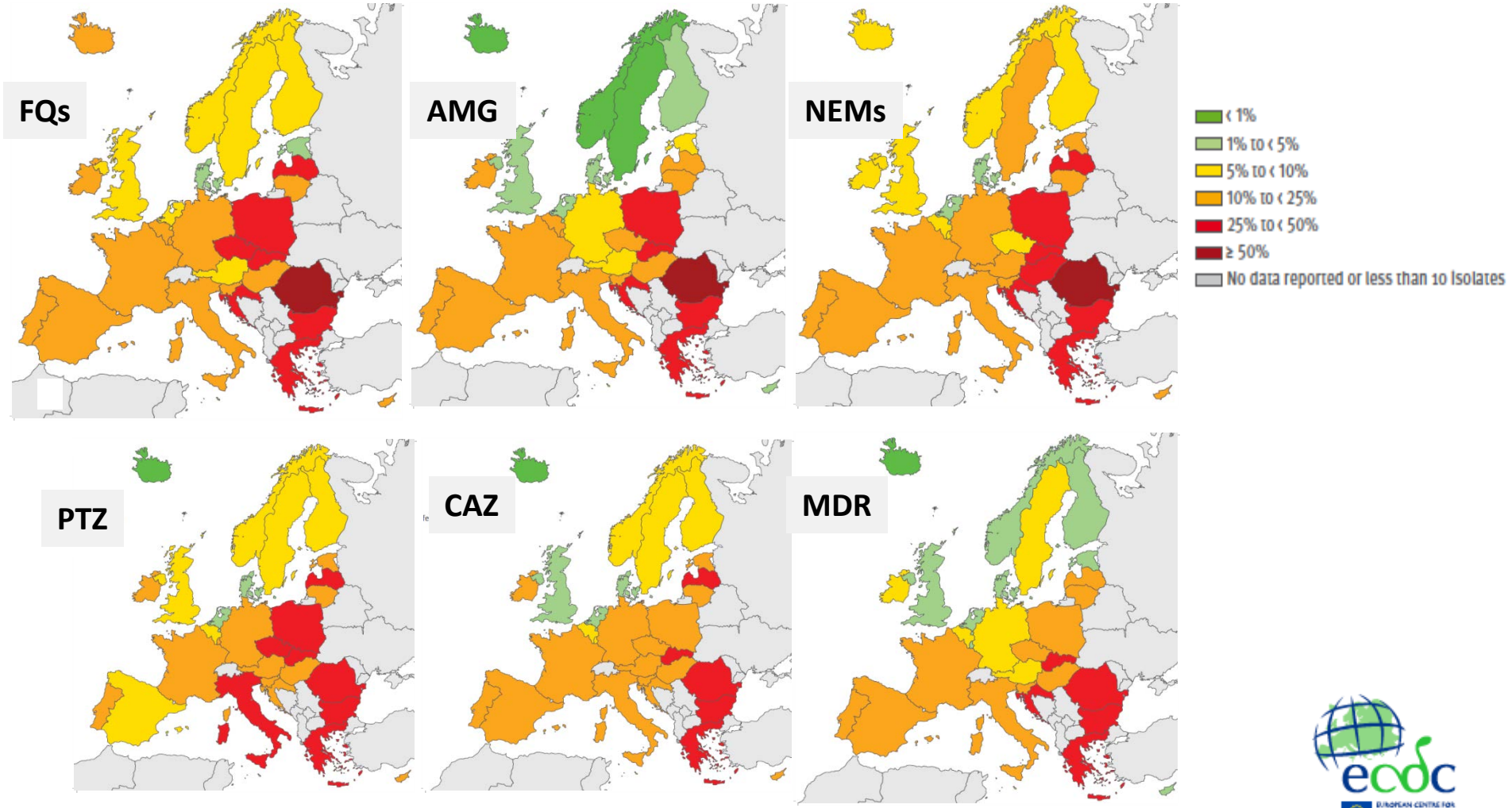
Broad Spectrum Against Gram-Negative Pathogens



INFEZIONI RESPIRATORIE COSA C'E' DI NUOVO: I BATTERI MULTIRESISTENTI

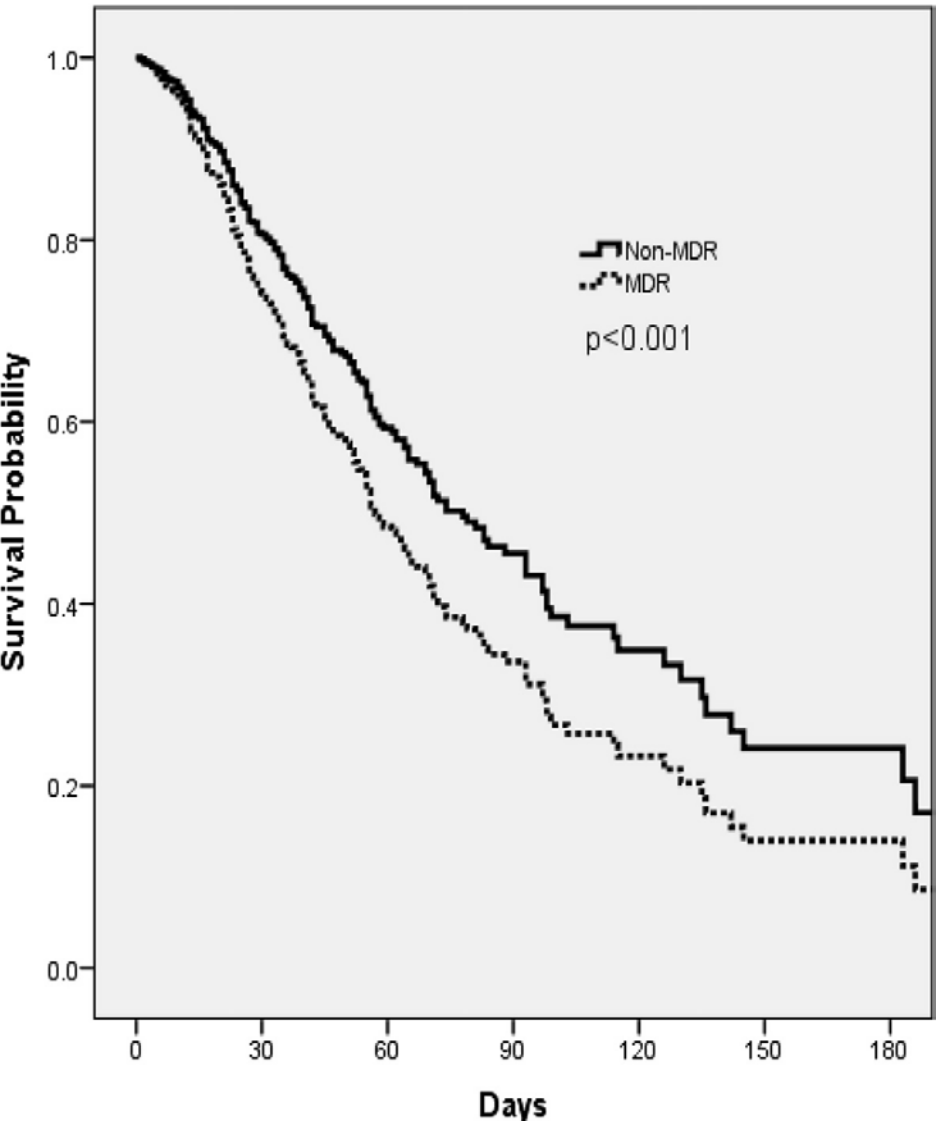
- Antibioticoresistenza un tema d'attualità
- Antibioticoresistenza e consumo/politica degli antibiotici → antimicrobial stewardship in pneumonia
- Nuovi farmaci per la gestione di MDR
  - Gram positivi
  - Gram negativi
    - Germi produttori di Carbapenemasi
    - Psudomonas multiresistente

Pseudomonas aeruginosa resistance in 2016



An international multicenter retrospective study of *Pseudomonas aeruginosa* nosocomial pneumonia: impact of multidrug resistance.

Micek ST et al, Crit Care. 2015;19:219.



MORTALITY

Cox proportional hazards model curve

Overall hospital mortality

35.7%

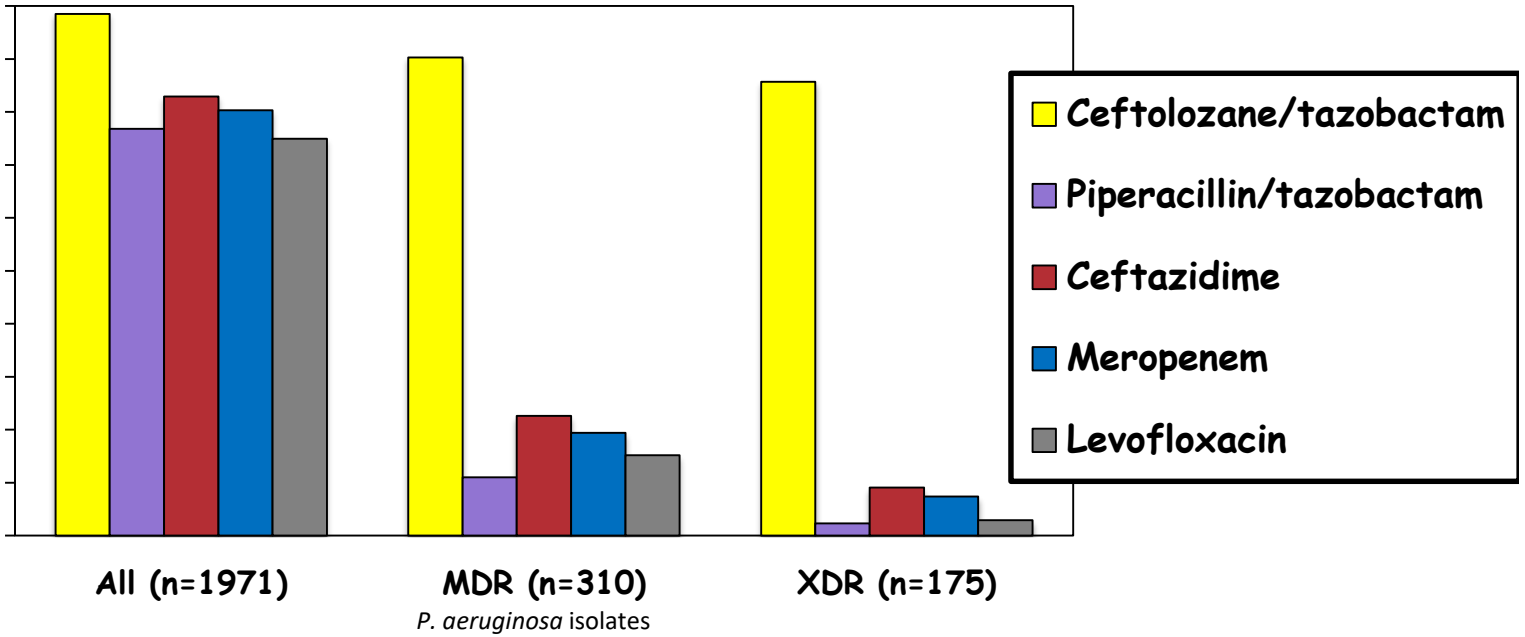
MDR 44.7%

non MDR 31.7 %

New drugs and usual clinical dosage for new anti-Pseudomonas agents.

Drug	Current clinical indications	Usual clinical dosage for serious infections	Other comment
Cephalosporins			
Cefiderocol	Complicated UTI	2 g intravenous every 8 hours	-
Cephalosporin + β-lactamase inhibitor			
Ceftolozane-tazobactam	Complicated UTI and IAI	Loading dose 1.5 g or 3 g intravenous in 1 hour, followed by 1.5 g or 3 g intravenous every 8 hours	Extended infusion (over 3 h) 1.5 g or 3 g every 8 hours is recommended
Ceftazidime-avibactam	Complicated UTI and IAI, HAP and VAP and Gram-negative infections when other treatments might not work	Loading dose 2.5 g intravenous in 1 hour, followed by 2.5 g intravenous every 8 hours	Extended infusion (over 3 h) 2.5 g every 8 hours is recommended
Carbapenem + β-lactamase inhibitor			
Meropenem-vaborbactam	Complicated UTI	2 g/2 g intravenous every 8 hours	Not active against MDR strains
Imipenem-relebactam	Not yet approved by any regulatory authority	500 mg/250 mg intravenous every 6 hours	Not active against MDR strains
Aminoglycoside			
Plazomicin	Not yet approved by any regulatory authority	15 mg/kg every 24 hours	-

In Vitro Activity of CEFTOLOZANE/TAZOBACTAM and Various Comparator Agents Against *P. aeruginosa* (US Hospitals 2011-2012)



	Ceftolozane/ tazobactam		Piperacillin/ tazobactam		Ceftazidime		Meropenem		Levofloxacin	
	MIC_{50}/MIC_{90}	%S*[a]	MIC_{50}/MIC_{90}	%S[b]	MIC_{50}/MIC_{90}	%S[b]	MIC_{50}/MIC_{90}	%S[b]	MIC_{50}/MIC_{90}	%S[b]
All (1971)	0.5/2	98.5	8/>64	76.8	2/32	82.9	0.5/8	80.3	0.5/>4	74.9
MDR (310)	2/8	90.3	>64/>64	11	32/>32	22.6	8/>8	19.4	>4/>4	15.2
XDR (175)	4/16	85.7	>64/>64	2.3	32/>32	9.1	8/>8	7.4	>4/>4	2.9

Farrell et al. Antimicrob Agents Chemother. 2013;57:6305-10.

Ceftolozane-tazobactam for the treatment of multidrug-resistant *Pseudomonas aeruginosa* infections: Clinical effectiveness and evolution of resistance

- Twenty-one patients were treated with ceftolozane-tazobactam for multidrug-resistant *Pseudomonas aeruginosa* infections, predominantly pneumonia.
- Thirty and 90-day mortality rates were 10% and 48%, respectively.
- Resistance emerged in 3 patients, which was associated with mutations in and/or increased expression of *ampC β*-lactamase

Haidar et al CID july 2017

Multicenter Evaluation of Ceftolozane/Tazobactam for Serious Infections Caused by Carbapenem-Resistant *P. aeruginosa*

Munita JM et al - Clin Infect Dis. 2017 Mar 14.

C/T was used in 35 patients with carbapenem-resistant *P. aeruginosa* infections.
Pneumonia was the most common diagnosis (n = 18 [51%])

Susceptibility testing for C/T was not performed in 5 cases.
Among the remaining 30 isolates: 26 (87%) were susceptible, 2 were intermediate, and 2 were fully resistant (with MICs of 16 µg/mL and 48 µg/mL).
Among 23 isolates R to all other β-lactams tested, C/T remained active against 19 (83%).

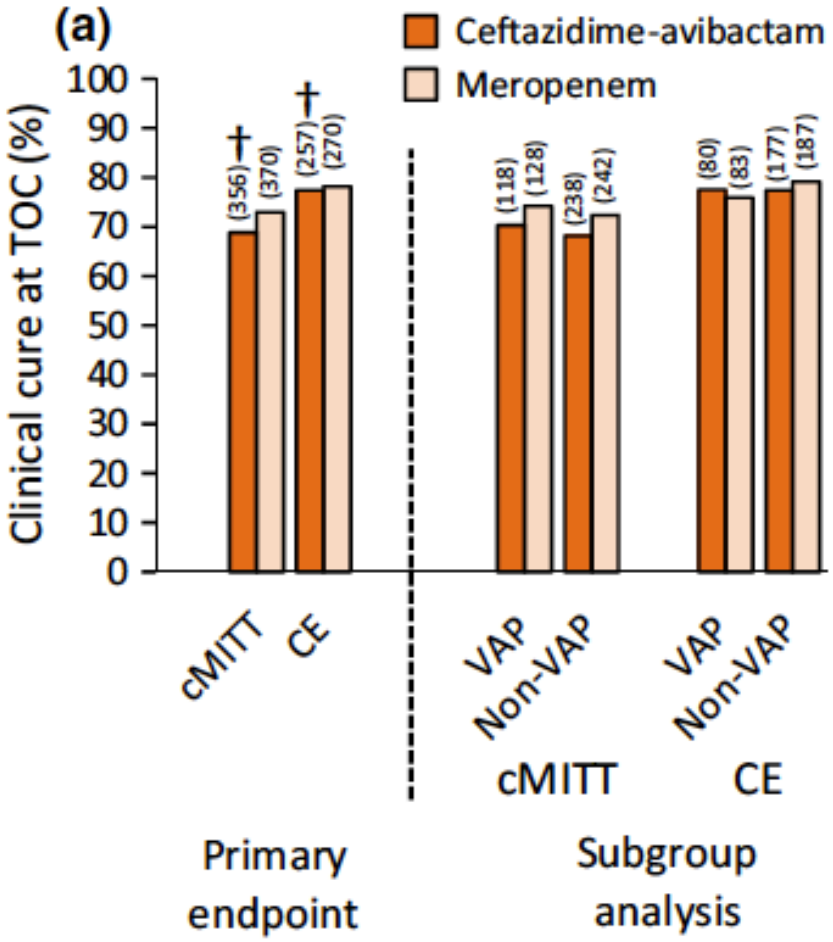
In 8 patients C/T was used in association with a second anti-pseudomonal drug:
- 5 pts an inhaled antibiotic (colistin or tobra)
- 2 pts cipro ev
- 1 pts colistin and tobra ev

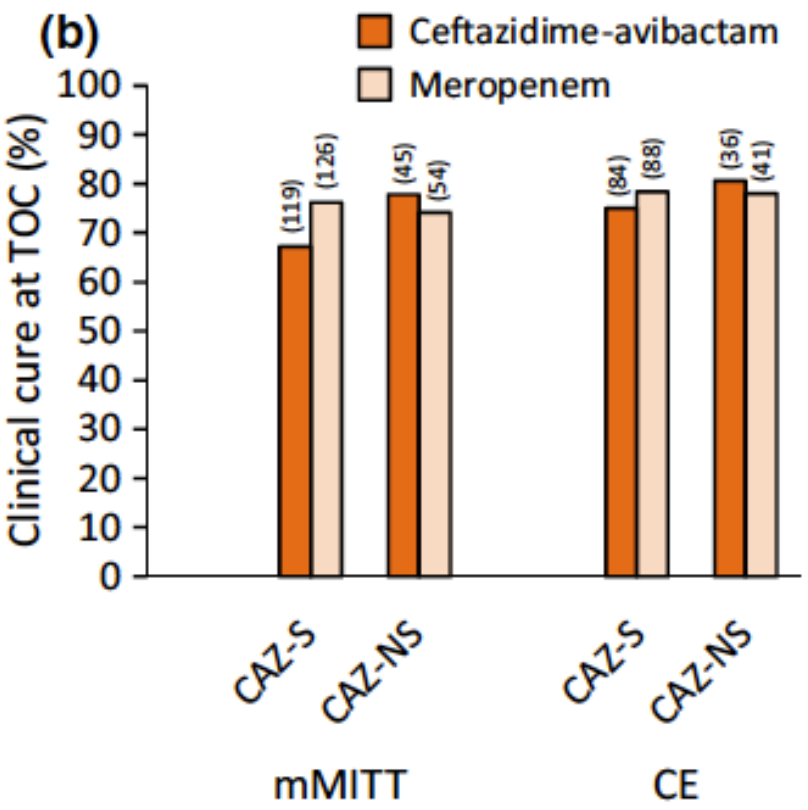
11 pts were treated with the approved dose of 1.5 g every 8 hours
9 pts received 3 g every 8 hours Others according to renal function

Treatment was considered successful using clinical standards in 26 (74%) of the 35 cases
Follow-up cultures were available in 25 patients, none of whom was found to have a microbiological failure.

Nine patients considered to have failed C/T therapy (in 3 patients failure was not directly attributed to C/T)

Clinical cure rates at test-of-cure visit in the phase III REPROVE trial in patients with hospital-acquired pneumonia (including VAP) treated with Ceftazidime Avibactam



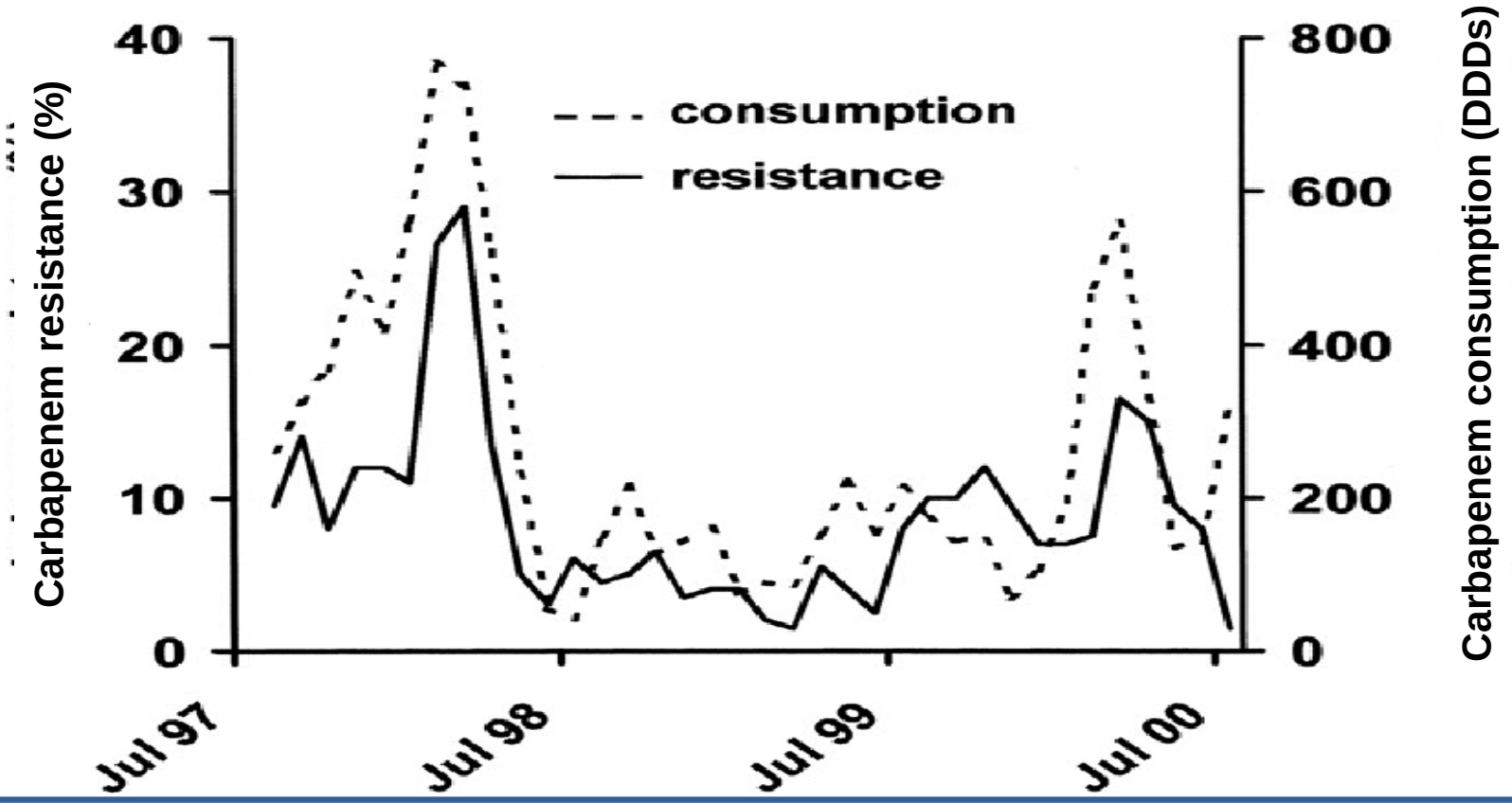


CE clinically evaluable population, cMITT clinically modified intent-to-treat population, mMITT microbiological modified intent-to-treat population

Primary efficacy and subgroup analyses By susceptibility of baseline isolates

Correlation Between Carbapenem Consumption and *P. aeruginosa* Resistance

Lepper PM, et al. *Antimicrob Agents Chemother*. 2002;46:2920-2925.



Nuovi farmaci , buone opportunità !
Ma non commettiamo gli errori del passato

INFEZIONI RESPIRATORIE COSA C'E' DI NUOVO: I BATTERI MULTIRESISTENTI

- **Livelli elevati antibioticoresistenza in Italia → Piano Nazionale sarà sufficiente?**
- **Oltre alle misure di contenimento delle infezioni e' necessaria un'antimicrobial stewardship anche nella gestione delle infezioni respiratorie**
- **Vi sono nuove opzioni terapeutiche per HAP da gram positivi → incertezza sul raporto costo beneficio**
- **Opzioni riemergenti, nuove opzioni già disponibili o in via di registrazione per il trattamento di gram negativi multiresistenti → impiego in combinazione con altri farmaci e con nuovo approccio diagnostico**
- **L'uso saggio delle opzioni terapeutiche riemergenti o nuove rappresenta un capitale per il futuro**