Clinica delle Malattie Infettive e Tropicali
Università degli Studi dell'Insubria –
ASST-Sette Laghi, Varese
"Second Opinion" Infettivologica
Centro Nazionale Trapianti, ISS, Roma

Sistema Socio Sanitario
Regione Lombardia
ASST Sette Laghi

Rete Nazionale Trapianti

Le nuove combinazioni di inibitori delle carbapenemasi-βlattamasi

Paolo Grossi

GIORNATE INFETTIVOLOGICHE LUIGI SACCO 2018
Milano, 14-15 giugno 2018

DISCLOSURES

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I, have the following relationships with commercial interests:

Grants/Research Support: MSD

Speakers Bureau/Honoraria: MSD, BIOTEST, GILEAD, ANGELINI, NOVARTIS, PFIZER, BD

Consulting Fees: MSD, BIOTEST, PARATEK, BD, ANGELINI

Antimicrobial Resistance

- Infectious diseases are among the top 10 causes of death and the leading cause of disability-adjusted life years worldwide.
- The emergence of pathogenic microbes with drug resistance, not only to the most commonly used antibiotics but also to second-line, “reserve” medicines, further increases the burden of infectious diseases.
- Low-income countries are particularly vulnerable because of conditions that enable the spread of these diseases, such as poor sanitation, lack of control of and guidance on antibiotic use, inadequate healthcare services and systems, and limited or inadequate infection control measures.
- Middle- and upper-middle-income countries are not free of the burden of drug resistance, however. BRICS countries and several European countries face major epidemics of multidrug-resistant infections caused by common Gram-negative bacteria and multidrug-resistant-TB (MDR-TB), with devastating public health and economic consequences.
- Sadly, the pipeline for new antibiotics currently includes only a small number of novel compounds in development.

GLOBAL PRIORITY LIST OF ANTIBIOTIC-RESISTANT BACTERIA TO GUIDE RESEARCH, DISCOVERY, AND DEVELOPMENT OF NEW ANTIBIOTICS

27 February, 2017

World Health Organization

WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

Priority 1: CRITICAL#

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

World Health Organization

GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE

- Antimicrobial resistance threatens the very core of modern medicine and the sustainability of an effective, global public health response to the enduring threat from infectious diseases.
- Effective antimicrobial drugs are prerequisites for both preventive and curative measures, protecting patients from potentially fatal diseases and ensuring that complex procedures, such as surgery and chemotherapy, can be provided at low risk.
- Antimicrobial resistance is a crisis that must be managed with the utmost urgency.
- **As the world enters the ambitious new era of sustainable development, we cannot allow hard-won gains for health to be eroded by the failure of our mainstay medicines.**

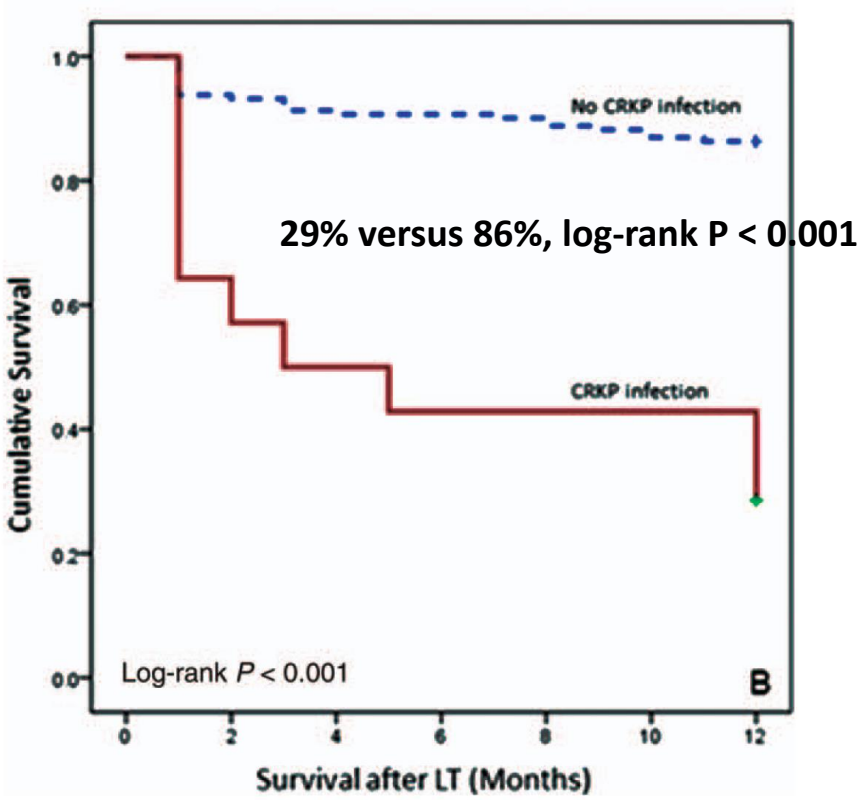
MDR Gram-negatives

- **ESBL = extended-spectrum β-lactamases**
- **CRA = carbapenem-R *Acinetobacter***
- **COS-Pa = colistin-only S *P. aeruginosa***
- **CRE = carbapenem-R Enterobacteria**
- **CCRE = colistin+carbapenem-R Enterobacteria**

Risk of Death is Higher in Patients Infected with Resistant Strains

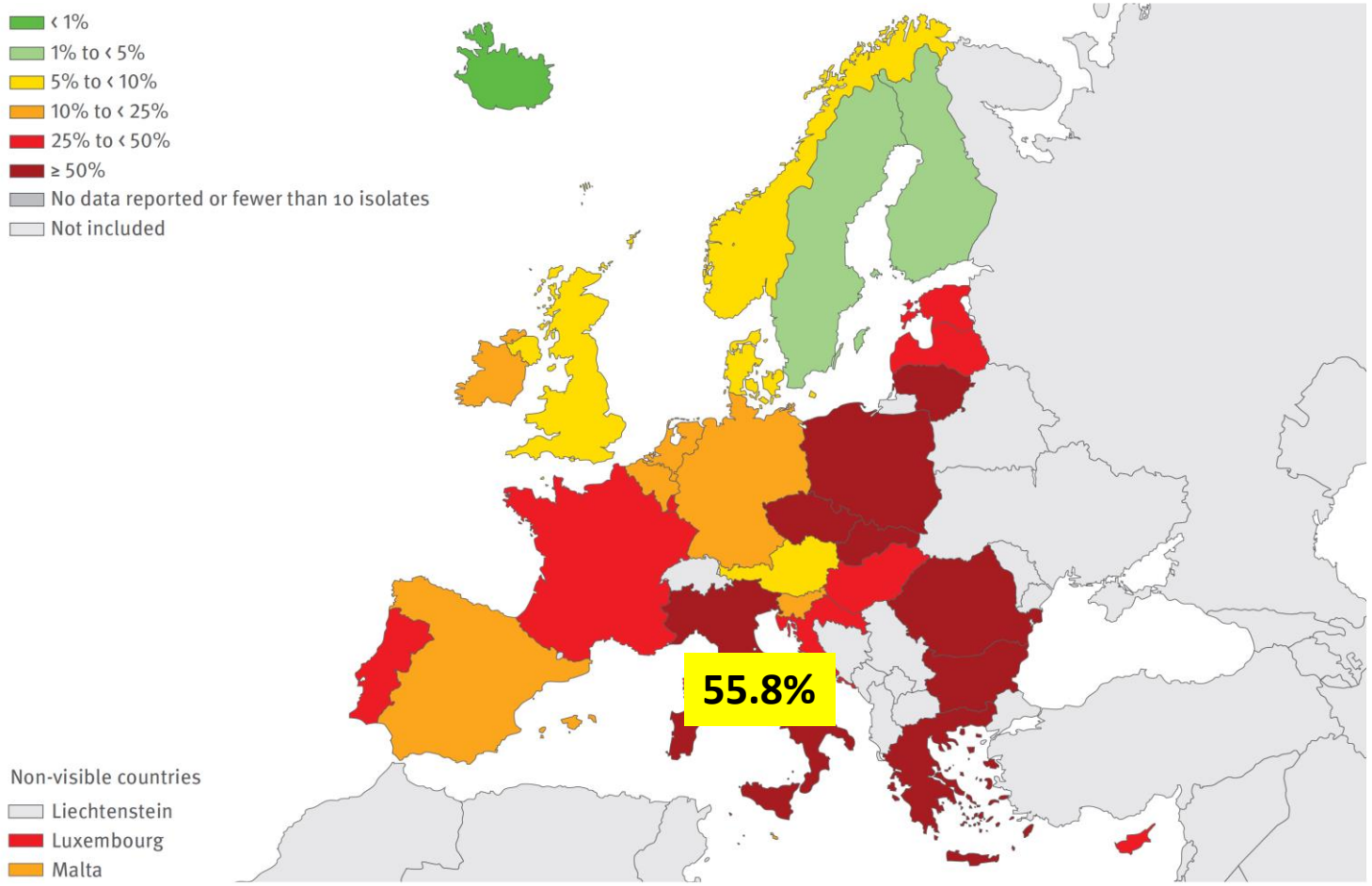
		Deaths (%)		
	Outcome (number of studies included)	**Resistant**	**Not resistant**	**RR (95% CI)**
***Escherichia coli* resistant to:**				
3rd gen. cephalosporins	Bacterium attributable mortality (n=4)	23.6	12.6	2.02 (1.41 to 2.90)
Fluoroquinolones	Bacterium attributable mortality (n=1)	0	0	
***Klebsiella pneumoniae* resistant to:**				
3rd gen. cephalosporins	Bacterium attributable mortality (n=4)	20	10.1	1.93 (1.13 to 3.31)
Carbapenems	Bacterium attributable mortality (n=1)	27	13.6	1.98 (0.61 to 6.43)
***Staphylococcus aureus* resistant to:**				
Methicillin (MRSA)	Bacterium attributable mortality (n=46)	26.3	16.9	1.64 (1.43 to 1.87)

Survival for LT recipients with CRKP infections versus LT recipients without CRKP infections

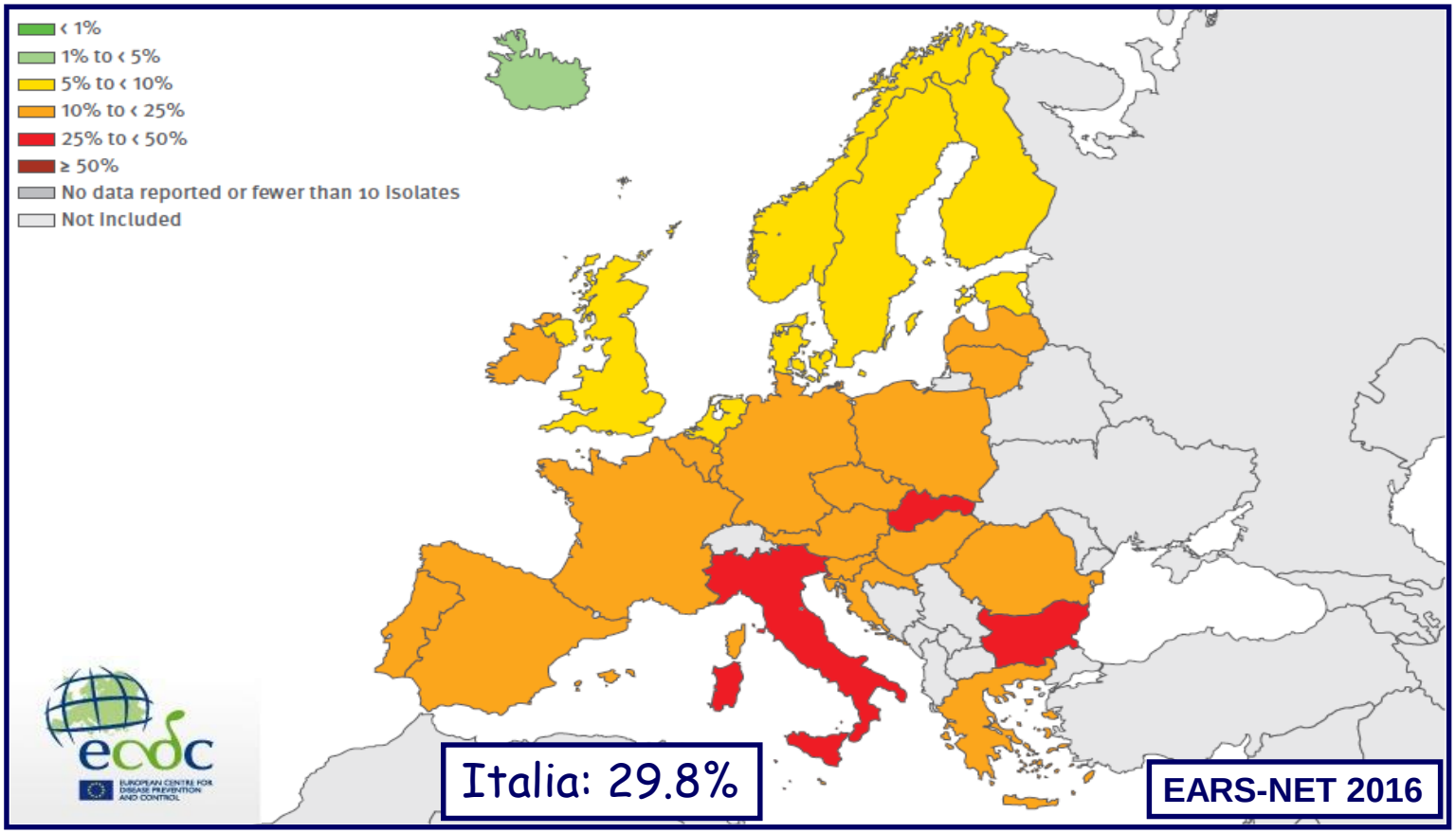


Jayant S. Kalpoe , et al. LIVER TRANSPLANTATION 18:468-474, 2012

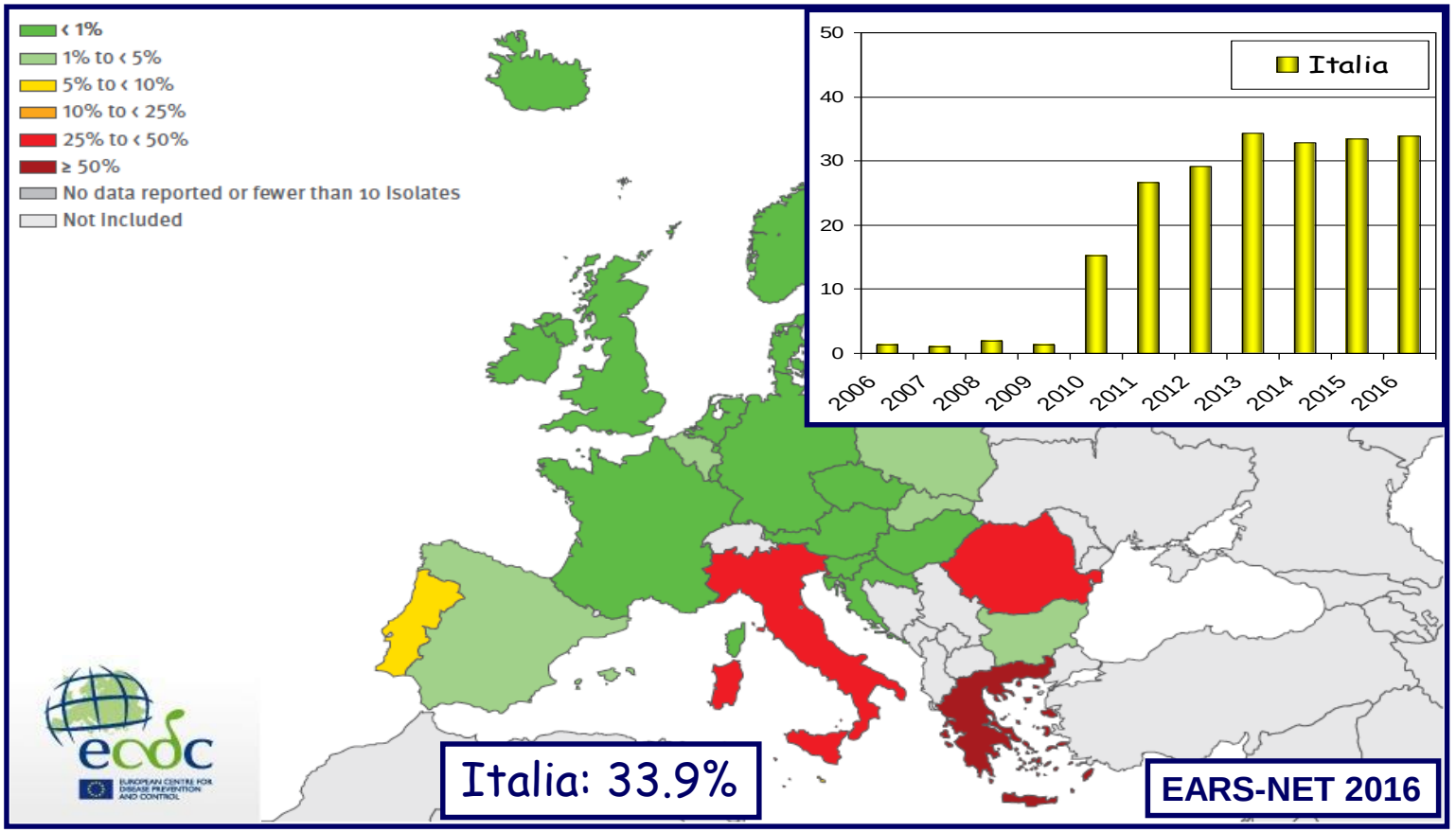
Klebsiella pneumoniae. Percentage (%) of invasive isolates with resistance to third-generation cephalosporins, by country, EU/EEA countries, 2016



Escherichia coli: resistenza alle cefalosporine 3G (2006-2016)



Klebsiella pneumoniae: resistenza ai carbapenemi (2006-2016)



	Italia 2015 (%) (categoria)[§]	Media europea 2015 (%) (categoria)[§]	**Trend 2012-15**[*]
Klebsiella pneumoniae			
resistente a cefalosporine 3° generazione	55,9 (6)	30,3 (5)	>
resistente agli aminoglicosidi	34,0 (5)	22,5 (4)	
resistente ai carbapenemi	33,5 (5)	8,1 (3)	
MDR (R a cefalosporine di 3° generazione + aminoglicosidi + fluorochinoloni)	29,7 (5)	18,6 (4)	
Escherichia coli			
resistente a cefalosporine 3° generazione	30,1 (5)	13,1 (4)	>
resistente a fluorochinoloni	44,4 (5)	22,8 (4)	>
resistente agli aminoglicosidi	20,2 (4)	10,4 (4)	
MDR (R a cefalosporine di 3° generazione + aminoglicosidi + fluorochinoloni)	14,6 (4)	5,3 (3)	

Therapy of MDR Pathogens

- Therapy of invasive infections due to multidrug-resistant *pathogens* is challenging, and some of the few active drugs are not available in many countries.
- For extended-spectrum β-lactamase and AmpC producers, carbapenems are the drugs of choice, but alternatives are needed because the rate of carbapenem resistance is rising.
- Potential active drugs include classic and newer β-lactam–β-lactamase inhibitor combinations, cephamycins, temocillin, aminoglycosides, tigecycline, fosfomycin, and, rarely, fluoroquinolones or trimethoprim-sulfamethoxazole.

Extended spectrum β-lactamase (ESBL)

- ESBLs are a large, rapidly evolving group of plasmid-enzymes that confer resistance to penicillins, first-, second-, and third generation cephalosporins, and aztreonam.
- They are inhibited by beta-lactamase inhibitors such as clavulanic acid.
- During recent years, antibacterial therapy became increasingly more complex. ESBL positive isolates are often associated with multidrug resistance (MDR) especially to fluoroquinolones, aminoglycosides and sulfonamides.
- Insertion sequences, integrons and transposons promiscuously transferred between bacteria played a crucial role in global dissemination of the most common ESBL genes, namely blaCTX-M.
- The prevalence of ESBL-producing organisms increased dramatically in the last decade in particular as an etiological agent in community-acquired infections, health care settings, nursing homes, and even veterinary settings

The Use of Noncarbapenem β-Lactams for the Treatment of Extended-Spectrum β-Lactamase Infections

Pranita D. Tamma[1] and Jesus Rodriguez-Baño[2]

- **βL-βLIs seems to be a reasonable options for low- to moderate-severity infections, those resulting from urinary or biliary sources, and infections with MICs <4 µg/mL.**
- **For critically-ill pts, those with higher inoculum infections, and elevated MICs, it might be more appropriate to administer carbapenem therapy, at least initially.**
- **If PTZ is administered to patients with invasive ESBL infections, we would recommend administering 4.5 g every 6 hours (or 4.5 g every 8 hours as extended infusion)**

Clinical Infectious Diseases® 2017;64(7):972–80

The Use of βL/βLIs for ESBL Infections:
Defining the Right Patient Population
Pranita D. Tamma, MD, MHS & Maria Virginia Villegas, MD, MSc

Caveat for βL/βLIs in invasive ESBL infections

- **In vitro observed inoculum effect**
- **Data from animal studies**
- **Co-expression of additional β-lactamases not effectively inhibited by β-lactamase inhibitors**
- **Concerns regarding inadequate PK/PD drug target attainment with standard β-lactam βL/βLI dosing regimens**

August 2017 Volume 61 Issue 8 e00164-17 Antimicrobial Agents and Chemotherapy

Table 1. Study Data Comparing the Treatment of Extended-Spectrum β-Lactamase Bloodstream Infections with BL/BLIs versus Carbapenems.[9,10,17-21]

Study	Empirical or Definitive	Number of Participants (BL/BLI vs Carbapenem)	Percentage Urinary Source or Biliary Tract (BL/BLI vs Carbapenem)	Percentage ICU (BL/BLI vs Carbapenem)	Percentage *Escherichia coli*	Mortality End Point (BL/BLI vs Carbapenem)
Rodríguez-Baño et al[9]	Empirical (n = 103)	72 vs 31	72.2% vs 58.1%	9.9% vs 6.7%	100%	9.7% vs 19.4% ($P > 0.20$)[a]
Gutiérrez-Gutiérrez et al[20] (2016)	Empirical (n = 365)	170 vs 195	60% vs 59%	7.6% vs 13.3%	72.3%	17.6% vs 20% (95% CI = −10.2% to 5.8%; $P = 0.6$)[a]
Gutiérrez-Gutiérrez et al[20] (2016)	Definitive (n = 601)	92 vs 509	52.2% vs 58%	4.3% vs 12.2%	73.0%	13.9% vs 9.8% (95% CI = −10.2% to 5.8%; $P = 0.28$)[a]
Gudiol et al[21] (2017)	Empirical (n = 174)	48 vs 126	6.9% Each	14.5% vs 23.8%	73.6%	20.8% vs 13.4% ($P = 0.33$)[a]
Gudiol et al[21] (2017)	Definitive (n = 251)	17 vs 232	6.9% Each	11.7% vs 18.8%	74.9%	5.8% vs 15.8% ($P = 0.99$)[a]

Conclusions: Completely sparing carbapenem therapy cannot be justified among patients with ESBL BSIs. Determining the source of infection is critical to identify patients for whom carbapenem-sparing therapy is appropriate.

Daniel B. Chastain, et al. Ann Pharmacother. 2017 Dec 1:1060028017748943. [Epub ahead of print]

RCT Meropenem vs Piperacillin-Tazobactam for Definitive Treatment of BSI's Due to Ceftriaxone Non-susceptible Escherichia Coli and Klebsiella Spp. (MERINO)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators.

⚠ Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT02176122

Recruitment Status : Terminated (Secondary to third interim analysis by the study DSMB.)

First Posted : June 26, 2014

Last Update Posted : November 27, 2017

28thECCMID	**EUROPEAN CONGRESS OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES**	**Madrid, Spain 21-24 Aprii 2018**

The MERINO Trial: piperacillin-tazobactam versus meropenem for the definitive treatment of bloodstream infections caused by third-generation cephalosporin non-susceptible *Escherichia coli* or *Klebsiella* spp.: an international multi-centre open-label non-inferiority randomised controlled trial

- **Results:** Between February 2014 and July 2017, 391 patients were enrolled, from 1,646 screened. Of these 379 were randomized appropriately, received at least one dose of study drug and were included in the modified intention to treat (mITT) population (piperacillin-tazobactam=188, meropenem=191).
- **Conclusions:** The use of **piperacillin-tazobactam as definitive therapy for BSI** caused by *E. coli* or *K. pneumoniae* with non-susceptibility to 3GCs **was inferior to meropenem and should be avoided** in this context.

Patrick Harris', et al. ECCMID 2018 Abstract #01121

The Use of Noncarbapenem β-Lactams for the Treatment of Extended-Spectrum β-Lactamase Infections

Pranita D. Tamma[1] and Jesus Rodriguez-Baño[2]

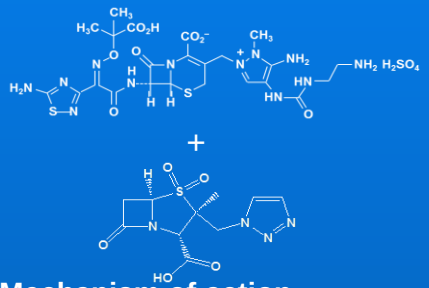
- **Ceftolozane** demonstrates good activity against Enterobacteriaceae but its activity is limited against ESBLs.
- **Tazobactam** is a potent, irreversible inhibitor of most ESBLs.
- **The MIC50/MIC90 of this agent for ESBL-producing *E. coli* are 0.5/4 µg/mL and for *K. pneumoniae* 4/>32 µg/mL**
- Differences in MIC distributions may be reflective of discrepancies in ESBL genes present.
- **The blaCTX-M genes predominate in *E. coli*, whereas there is often a preponderance of blaTEM/SHV in *K. pneumoniae*, with variations in local epidemiology.**

Clinical Infectious Diseases® 2017;64(7):972–80

Ceftolozane/Tazobactam Overview

Class

- Antipseudomonal cephalosporin + β-lactamase inhibitor
- Fixed 2:1 ratio



Mechanism of action

- Rapidly bactericidal
- Inhibits cell wall synthesis
- Active against organisms with porin deficiencies or mutations
- Inhibits β-lactamases, broadens coverage to most ESBL-producing Enterobacteriaceae

In vitro activity

- *Pseudomonas aeruginosa*, including drug-resistant strains
- *Escherichia coli*, including ESBL-positive strains
- *Klebsiella pneumoniae*, including ESBL-positive strains
- Minimal activity against Gram-positive bacteria
- Limited activity against anaerobes
- **No activity against KPC, MBL**

Development stage

- Completed Phase 3 trials for treatment of cIAI and cUTI
- Phase 3 trial underway for nosocomial pneumonia

In vivo efficacy

- Activity in mouse models of sepsis, pneumonia, urinary tract infection, burn wound infection, and thigh infection
- Positive outcomes and adhered to an expected safety profile in Phase 2 and 3 trials in adult patients with cUTI and cIAI

Pharmacokinetics

- Linear PK
- Lung penetration
- Rapid tissue distribution
- Minimal accumulation
- Extensive renal excretion
- Low protein binding
- Minimal CYP450 drug-drug interactions

Zhanel et al. *Drugs.* 2014;74:31-51.

Ceftolozane/Tazobactam

Il farmaco è registrato per le seguenti indicazioni:

- **Infezioni intra-addominali complicate (c-IAI), in associazione al metronidazolo**
- **Infezioni complicate delle vie urinarie (c-UTI)**
- **Somministrazione IV alla dose di 1,5 g ogni 8 ore**
- ***Il farmaco è prescrivibile soltanto dallo specialista infettivologo o da clinico designato dal CIO, e viene fornito dalla Farmacia previa compilazione della scheda AIFA***

ALLEGATO *1*

Scheda cartacea per la prescrizione della specialità medicinale ZERBAXA (ceftolozano-tazobactam)

Indicazioni terapeutiche: Zerbaxa è indicato per il trattamento delle seguenti infezioni negli adulti:

- Infezioni intra-addominali complicate
- Pielonefrite acuta
- Infezioni complicate del tratto urinario

Devono essere considerate le linee guida ufficiali sull'uso appropriato degli agenti antibatterici.

La rimborsabilità è limitata alla pielonefrite acuta, alle infezioni complicate del tratto urinario sostenute da batteri gram-negativi resistenti ai trattamenti di prima linea e alle infezioni addominali complicate, la cui etiologia documentata o sospetta è dovuta a batteri gram-negativi resistenti ai trattamenti di prima linea.

La prescrivibilità è riservata allo specialista infettivologo o, in sua assenza, ad altro specialista con competenza infettivologica ad hoc identificato dal Comitato Infezioni Ospedaliere (CIO)

trattamenti di prima linea (Allegare antibiogramma)	

PROGRAMMA TERAPEUTICO

Farmaco	Specialità	Dose	Durata prevista
Zerbaxa	1g./0,.5g. polvere per concentrato per soluzione per infusione		

Il dosaggio standard in soggetti con CrCl>50 mL/min è 1 g. ceftolozano/0,5 g. tazobactam ogni 8 ore (tempo di infusione: 1 h.) per una durata di 4-14 giorni nel trattamento delle cIAI e di 7 giorni nel trattamento della pielonefrite acuta e delle cUTI.

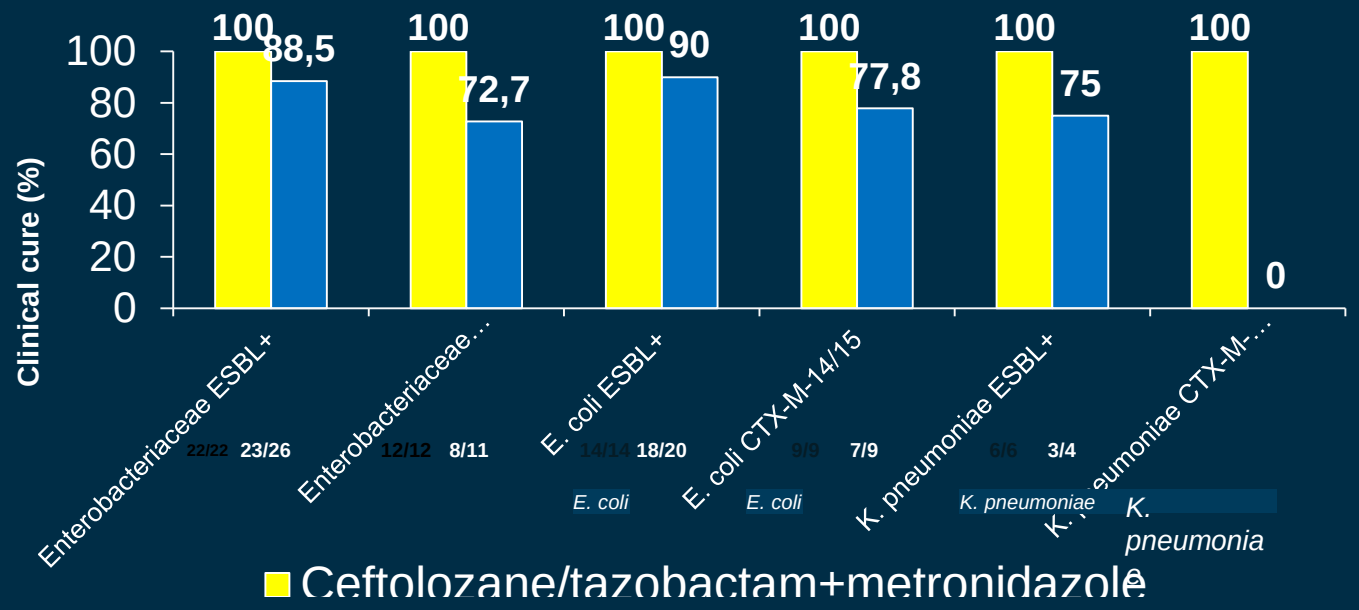
Nome e cognome del Medico*: _____

Recapiti del Medico*: _____

** La prescrivibilità è riservata allo specialista infettivologo o, in sua assenza, ad altro specialista con competenza infettivologica ad hoc identificato dal Comitato Infezioni Ospedaliere (CIO) istituito per legge presso tutti i presidi ospedalieri (Circolare Ministero della Sanità n. 52/1985).*

TIMBRO E FIRMA DEL MEDICO RICHIEDENTE

ASPECT-cIAI
Clinical Response by ESBL Status (ME at TOC)



CTX-M-14/15 is a subset of ESBL-producers.
cIAI, complicated intra-abdominal infection; *E. coli, Escherichia coli*; ESBL, extended-spectrum β-lactamase; *K. pneumoniae, Klebsiella pneumoniae*; ME, microbiologically evaluable; TOC, test of cure.
Eckmann et al. ECCMID 2 2014. Poster P0266a.

Ceftolozane/Tazobactam
Proposed Dosing Based on Pharmacokinetic Studies

	cIAI	cUTI	NP/VAP
CrCL >50 mL/min	1.5 g q8h	1.5 g q8h	3 g q8h
CrCL 30-50 mL/min	750 mg q8h	750 mg q8h	1.5 g q8h
CrCL 15-30 mL/min	375 mg q8h	375 mg q8h	750 mg q8h
Hemodialysis	750 mg loading dose, 150 mg q8h	750 mg loading dose, 150 mg q8h	ND

Current Formulation

Ceftolozane	1000 mg active
Tazobactam sodium	500 mg active
Citric acid	21 mg
L-Arginine	615.4 mg
NaCl	484.2 mg

Reconstituted with 10 mL 0.9% NaCl or sterile water for injection (SWFI) and further diluted in 100 mL 0.9% NaCl or SWFI and infused over 1 h

CrCL, creatinine clearance; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; NaCl, sodium chloride; NP, nosocomial pneumonia, q8h, every 8 hours; VAP, ventilator-associated pneumonia.
Data on file, Cubist Pharmaceuticals.

The Use of Noncarbapenem β-Lactams for the Treatment of Extended-Spectrum β-Lactamase Infections

Pranita D. Tamma[1] and Jesus Rodriguez-Baño[2]

Clinical Infectious Diseases® 2017;64(7):972–80

- **Ceftazidime-avibactam** is active in vitro against ESBL producers microorganisms
- **The MIC50/MIC 90 for ESBL-producing *E. coli* are 0.12/0.25 µg/mL and for *K. pneumoniae* 0.5/1 µg/mL**
- Phase 2/3 studies compared ceftazidime-avibactam (plus metronidazole) vs meropenem for intra-abdominal infections, but did not specifically compare outcomes of ESBL-confirmed pathogens.
- Data from a phase 3 study comparing ceftazidime-avibactam and doripenem in UTIs showed similar microbiological response for ceftazidime-resistant Enterobacteriaceae, most of which were ESBL producers

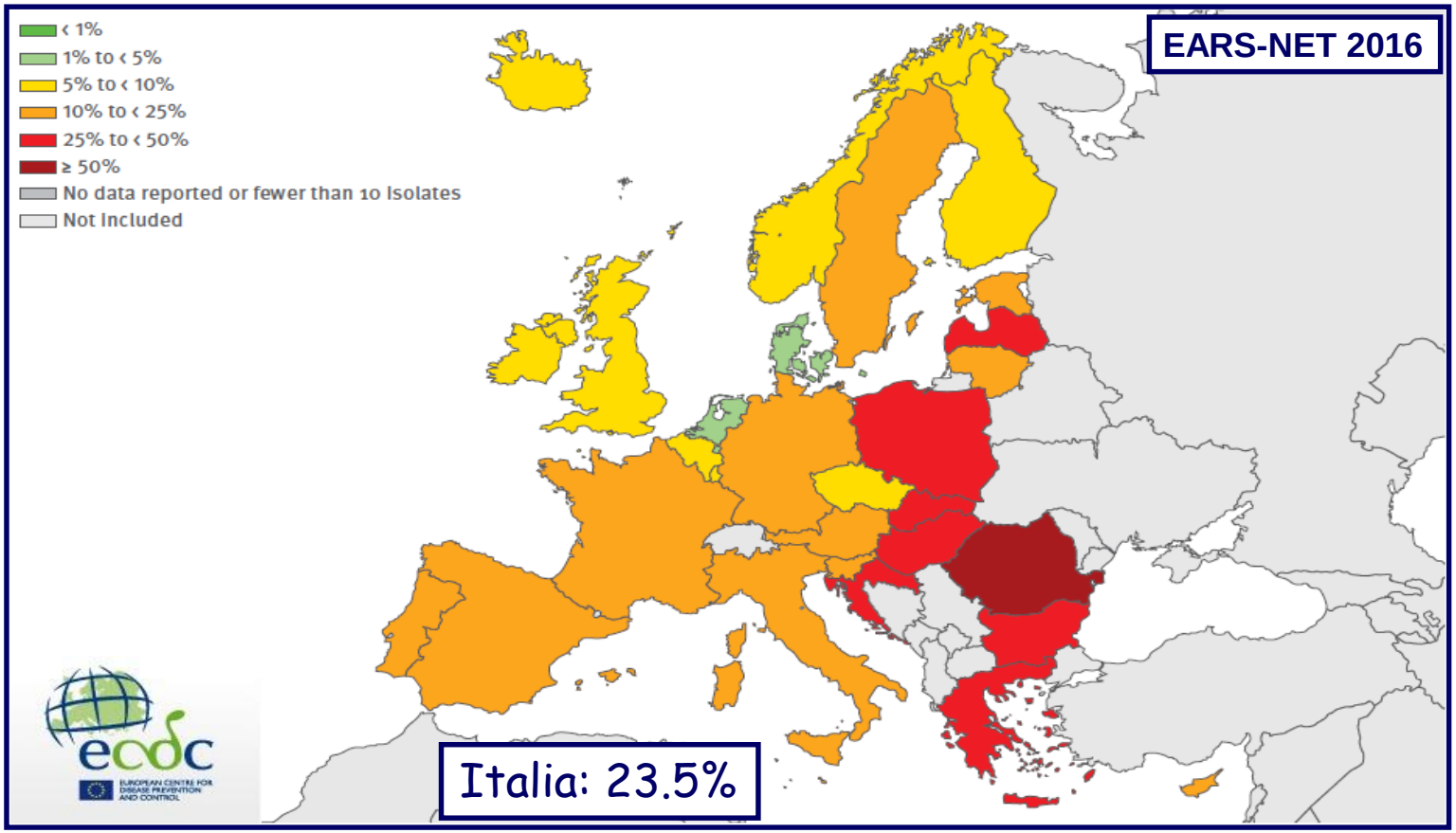
Treatment of Infections Caused by Extended-Spectrum-Beta-Lactamase-, AmpC-, and Carbapenemase-Producing *Enterobacteriaceae*

Jesús Rodríguez-Baño,[a] Belén Gutiérrez-Gutiérrez,[a] Isabel Machuca,[b] Alvaro Pascual[a]

- The available data support the efficacy of both new BLBLIs against susceptible ESBL producers in patients with cUTI, and also against cIAI.
- However, because of their potential added value against XDR organisms (XDR *P. aeruginosa* in the case of ceftolozane-tazobactam and KPC- or OXA-48-producing *Enterobacteriaceae* in the case of ceftazidime-avibactam), **it seems prudent to reserve these drugs for these particular organisms**.

April 2018 Volume 31 Issue 2 e00079-17 Clinical Microbiology Reviews

Pseudomonas aeruginosa: resistenza ai carbapenemi



Italian nationwide survey on *Pseudomonas aeruginosa* from invasive infections: activity of ceftolozane/tazobactam and comparators, and molecular epidemiology of carbapenemase producers

Tommaso Giani[1,2], Fabio Arena[1], Simona Pollini[1,2], Vincenzo Di Pilato[3], Marco Maria D'Andrea[1,2], Lucia Henrici De Angelis[1], Matteo Bassetti[4] and Gian Maria Rossolini[2,5]* on behalf of the *Pseudomonas aeruginosa* Working Group†

Table 2. MIC_{50} and MIC_{90} (mg/L) of ceftolozane/tazobactam and comparators for the collected isolates (935 in total)

	CTZ	FEP	CAZ	TZP	MEM	IPM	CIP	CST	AMK
MIC_{50}	1	4	4	16	1	2	0.25	2	4
MIC_{90}	4	32	64	>128	32	32	>16	4	16
%S	90.9	71.1	70.4	59.9	65.3	65.7	65.1	84.7	88.0

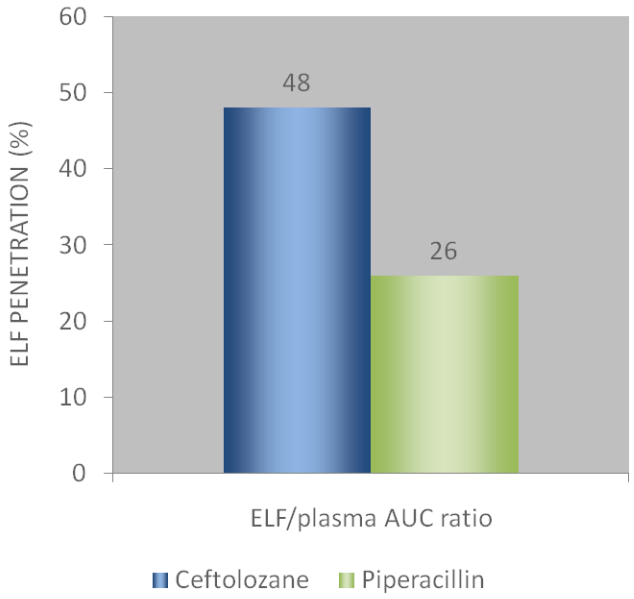
CTZ, ceftolozane/tazobactam (tazobactam at fixed concentration of 4 mg/L); FEP, cefepime; CAZ, ceftazidime; TZP, piperacillin/tazobactam (tazobactam at fixed concentration of 4 mg/L); MEM, meropenem; IPM, imipenem; CIP, ciprofloxacin; CST, colistin; AMK, amikacin; %S, percentage of susceptible isolates.

Results: Ceftolozane/tazobactam was the most active molecule, retaining activity against 90.9% of *P. aeruginosa* isolates, followed by amikacin (88.0% susceptibility) and colistin (84.7% susceptibility). Overall, 48 isolates (5.1%) were positive for carbapenemase genes, including bla_{VIM} ($n = 32$), bla_{IMP} ($n = 12$) and bla_{GES-5} ($n = 4$), while the remaining ceftolozane/tazobactam-resistant isolates tested negative for carbapenemase production. Carbapenemase producers belonged to 10 different STs, with ST175 ($n = 12$) and ST621 ($n = 11$) being the most common lineages. Genome analysis revealed different trajectories of spread for the different carbapenemase genes.

Journal of Antimicrobial Chemotherapy doi:10.1093/jac/dkx453

How Well Does Ceftolozane/Tazobactam Penetrate the Lung?

- 51 healthy adults received
  - 1.5 g ceftolozane/tazobactam q8h (60-min infusion)
  - 4.5 g piperacillin/tazobactam q6h (30-min infusion)
- **Ceftolozane penetrated well into the ELF** of healthy volunteers (**48%**)
  - Compared favorably to piperacillin (26%)
- Tazobactam penetration was
  - 44% when given with ceftolozane
  - 54% when given with piperacillin



AUC = area under the curve; ELF = epithelial lining fluid; q6h/q8h = every 6/8 hours.

Chandorkar G, et al. *J Antimicrob Chemother.* 2012;67:2463-2469.

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Safety and Efficacy Study of Ceftolozane/Tazobactam to Treat Ventilated Nosocomial Pneumonia (MK-7625A-008) (ASPECT-NP)

This study is currently recruiting participants. (see Contacts and Locations)

Verified March 2017 *by Cubist Pharmaceuticals LLC*

Sponsor:

Cubist Pharmaceuticals LLC

Information provided by (Responsible Party):

Cubist Pharmaceuticals LLC

ClinicalTrials.gov Identifier:

NCT02070757

First received: February 19, 2014

Last updated: March 8, 2017

Last verified: March 2017

History of Changes

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING
European Society of Clinical Microbiology and Infectious Diseases

8 November 2016

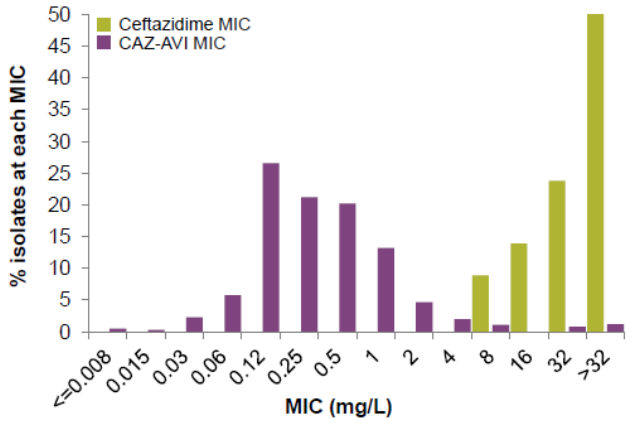
Clinical breakpoints for ceftazidime-avibactam[1]

Organism group	MIC breakpoints (mg/L)		Disk content (µg)	Zone diameter breakpoints (mm)	
	S ≤	R >		S ≥	R <
Enterobacteriaceae	8	8	**10-4**	13	13
Pseudomonas aeruginosa	8	8	**10-4**	17	17
PK-PD breakpoints	8	8	**-**	-	-

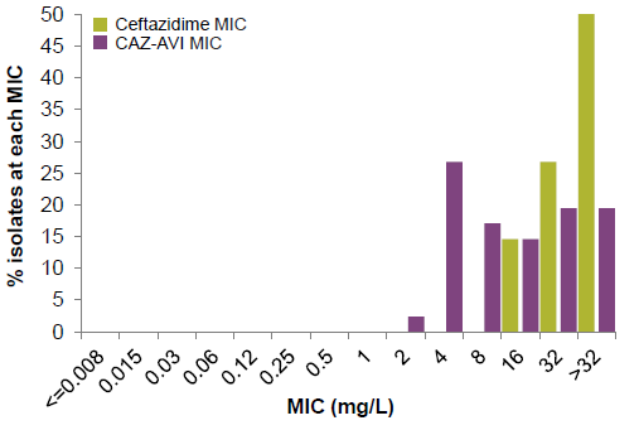
[1] For susceptibility testing purposes, the concentration of avibactam is fixed at 4 mg/L.

Baseline *in-vitro* activity of ceftazidime and ceftazidime-avibactam, mMITT population

Ceftazidime-resistant *Enterobacteriaceae*
n=642



Ceftazidime-resistant *P. aeruginosa*
n=41



MIC, minimum inhibitory concentration

Studio italiano di sorveglianza su *Pseudomonas aeruginosa* (20 centri, 2013-2014)

Isolati non-replicati da BSI o HAP/VAP (n = 935)

Isolati resistenti

a tutti i beta-lattamici = 20%

Isolati produttori di

metallo-beta-lattamasi = 4.7%

Courtesy of F.Luzzaro

Ceftolozane/Tazobactam Therapy of Respiratory Infections due to Multidrug-Resistant *Pseudomonas aeruginosa*

Table 1. Characteristics of Patients Treated With Ceftolozane-Tazobactam for Pneumonia due to *Pseudomonas aeruginosa*

Age and Sex	Susceptibilities (MIC, μg/mL)	Prior Antibiotic Therapy	Duration of Treatment With C/T	Clinical Outcome	Microbiologic Outcome	Significant Comorbid Conditions
69 y, male	C/T (0.25) Meropenem (>8) Cefepime (8) Ciprofloxacin (>2) Piperacillin/tazobactam (<16) Tobramycin (<2)	Ciprofloxacin	14 d	Cure	Eradication	Esophageal cancer Tracheostomy for respiratory failure
63 y, male	C/T (1) Meropenem (>8) Cefepime (>16) Ciprofloxacin (>2) Piperacillin/tazobactam (>64) Tobramycin (>8) Colistin (susceptible) Polymyxin (susceptible)	Meropenem Ciprofloxacin	14 d	Cure	Eradication	Polyneuropathy Chronic corticosteroid use History of cardiopulmonary arrest Tracheostomy for respiratory failure
52 y, male	C/T (1) Meropenem (>8) Cefepime (16) Ciprofloxacin (<0.5) Piperacillin/tazobactam (>16) Tobramycin (<2)	Meropenem Linezolid	10 d	Cure	Eradication	AIDS (absolute CD4 count of 59 cells/μL) *Clostridium difficile*–associated diarrhea with colon perforation and intra-abdominal abscess Respiratory failure

Abbreviations: C/T, ceftolozane/tazobactam; MIC, minimum inhibitory concentration.

Michael S. Gelfand and Kerry O. Cleveland. CID 2015;61:853

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

- A multicenter, retrospective study of patients infected with carbapenem-resistant Pseudomonas aeruginosa who were treated with ceftolozane/tazobactam was performed.
- Among 35 patients, pneumonia was the most common indication and treatment was successful in 26 (74%).
- Treatment failure was observed in all cases where isolates demonstrated ceftolozane-tazobactam minimum inhibitory concentrations ≥8 µg/mL.

Jose M. Munita, et al. Clinical Infectious Diseases® 2017;00(00):1–4

Carbapenemases

- Carbapenemases are β-lactamases capable of hydrolyzing carbapenems
  - Class A, B and D carbapenemases have been observed
    - Class A carbapenemases include KPCs
    - All class B metallo-β-lactamases are carbapenemases and include VIM, IMP and NDM
    - Class D carbapenemases include OXAs
- Overproduction of class C β-lactamase, can lead to carbapenem resistance in the absence of a carbapenemase
  - This is particularly the case when these β-lactamases are combined with other resistance mechanisms (e.g. porin loss)

KPC, *Klebsiella pneumoniae* carbapenemases.
Papp-Wallace KM, et al. Antimicrob Agents Chemother 2011;55:4943–60.

CRE Therapeutic Options

- **<u>Source control</u>**
- **Ceftazidime-Avibactam**
- **Meropenem-Vaborbactam (US)**
- Colistin
- Tygecycline
- Fosfomycin
- Colistin + Carbapenem
- Colistin + Carbapenem + Tygecycline
- Double Carbapenem ±

<u>Investigational</u>

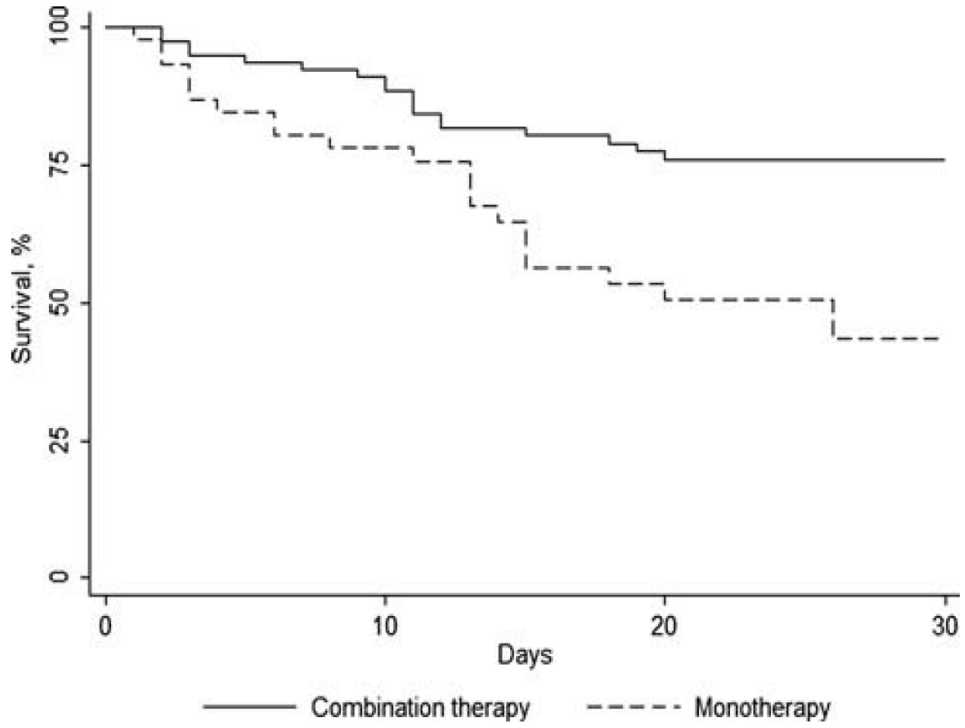
- *Imipenem-Relebactam*
- *Meropenem-Vaborbactam (EU)*
- *Eravacycline*
- *Plazomycin*
- *Cefiderocol (S-649266)*

Combination therapy for KPC infections

- The overall success rate of combination therapy was significantly higher than that of monotherapy (p 0.01; OR 2.41; 95% CI 1.2–4.7).
- The antibiotics most frequently used in combination therapy, in descending order, were colistin (n = 63), aminoglycosides (n = 46), carbapenems (n = 30), tigecycline (n = 26), aztreonam (n = 2), and tetracyclines (n = 2).
- It is of note that, on division of the patients who received combination therapy into two groups on the basis of the inclusion of a carbapenem in the regimen, it was shown that the carbapenem-containing regimens were significantly more efficacious than the non-carbapenem-containing regimens (p 0.04; OR 5.15; 95% CI 1.1–24.5).

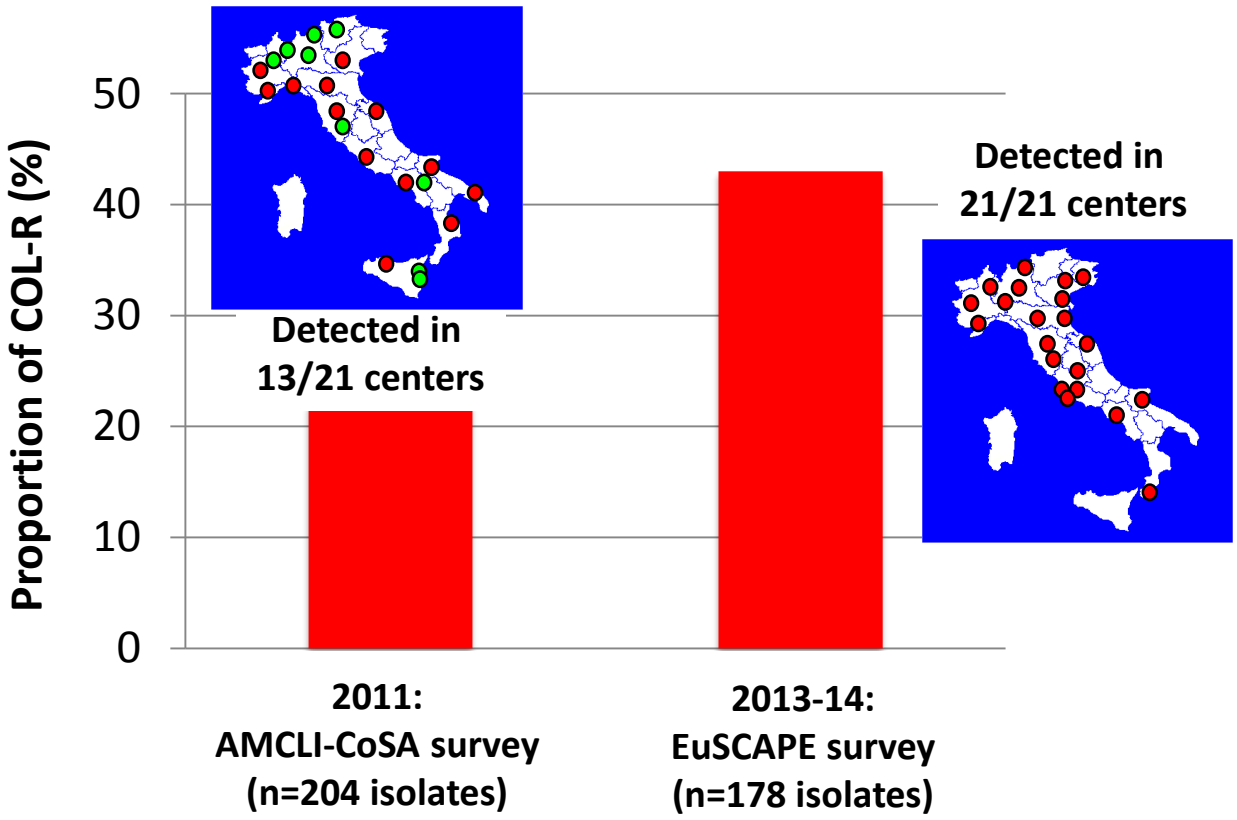
Akova M, et al, CMI, 2012;18:439–448

Impact of combination therapy versus monotherapy on 30-day mortality of patients with carbapenemase–producing K. pneumoniae isolate bloodstream infections (P = .002).



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

Colistin resistance among KPC+ *Klebsiella* from two nationwide surveys, Italy



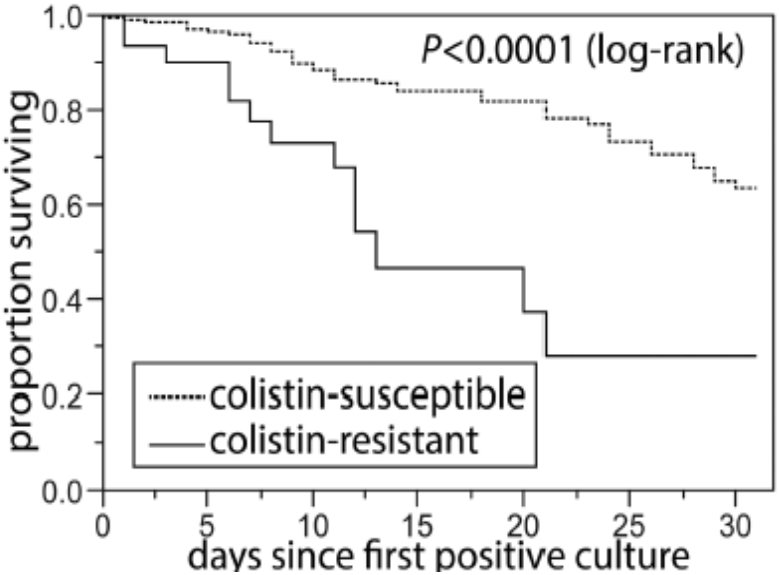
Giani *et al*. - Eurosurv 2013
Monaco *et al.* Eurosurv 2014

Clinical Infectious Diseases

MAJOR ARTICLE

Colistin Resistance in Carbapenem-Resistant *Klebsiella pneumoniae*: Laboratory Detection and Impact on Mortality

Laura J. Rojas,[1,2,3] Madiha Salim,[4] Eric Cober,[5] Sandra S. Richter,[6] Federico Perez,[3,7] Robert A. Salata,[7] Robert C. Kalayjian,[8] Richard R. Watkins,[9,10] Steve Marshall,[3] Susan D. Rudin,[1,3] T. Nicholas Domitrovic,[1,3] Andrea M. Hujer,[1,3] Kristine M. Hujer,[1,3] Yohei Doi,[11] Keith S. Kaye,[4] Scott Evans,[12] Vance G. Fowler Jr,[13,14] Robert A. Bonomo,[1,2,3,7,15,16] and David van Duin[17]; for the Antibacterial Resistance Leadership Group

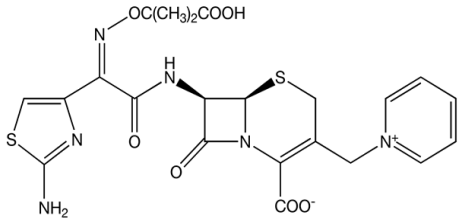


Rojas LJ, et al. Clin Infect Dis 2017;64:711–718.

Ceftazidime–avibactam

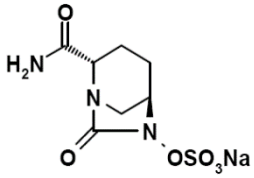
Ceftazidime

- Extended-spectrum cephalosporin with activity against Enterobacteriaceae and *P. aeruginosa*[1]
- Binds PBPs, leading to bacterial cell lysis[1]



Avibactam

- Novel non-β-lactam β-lactamase inhibitor with a unique mode of action[2]
- High binding affinity for Class A, C and some Class D β-lactamases (ESBLs, KPCs and AmpC), some of which are resistant to current agents (e.g. KPCs)[3]



Ceftazidime–avibactam is the first BL/BLI to retain activity against KPC-producing isolates, along with ESBLs, Ampc, and OXA-48

BL/BLI, β-lactam β-lactamase inhibitor; ESBL, extended-spectrum beta-lactamases; KPC, *Klebsiella pneumoniae* carbapenemase; PBP, penicillin binding proteins.

1. Hayes MV, Orr DC. J Antimicrob Chemother. 1983;12:119–126; 2. Ehmann DE et al. Proc Natl Acad Sci. 2012;29:11663–11668; 3. Aktaş Z, et al. Int J Antimicrob Agents 2012;39:86-9.

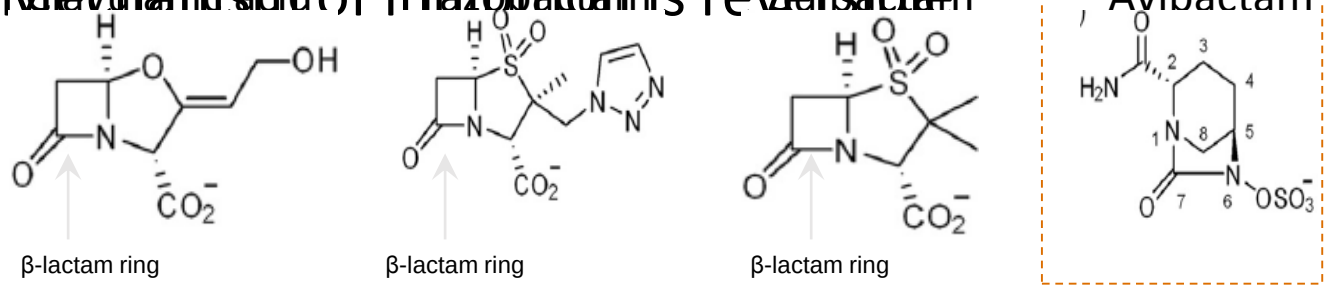
Ceftazidime–avibactam – Therapeutic indications

1. Complicated intra-abdominal infection (cIAI)
2. Complicated urinary tract infection (cUTI), including pyelonephritis
3. Hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP)
4. For the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options (after consultation with a physician with appropriate experience)

Avibactam: first in class of novel β-lactamase inhibitors

- Avibactam is a novel, first-in-class, non-β-lactam β-lactamase inhibitor from a new chemical class, diazabicyclooctane (DABCOs)
- The older β-lactamase inhibitors, clavulanic acid, tazobactam and sulbactam are all structurally related to β-lactams, caused acylation & subsequent irreversible inactivation of the β-lactamase (suicidal inhibition)
- Avibactam differs from these agents in all three respects
  - Does not have a β-lactam skeleton, instead it is a DABCO, so low propensity for hydrolysis
  - Expanded spectrum of β-lactamase inhibition
  - Mechanism of inhibition is reversible

Clavulanic acid Tazobactam Sulbactam Avibactam



Lahiri SD, et al. Antimicrob Agents Chemother 2013;57:2496–505.

Avibactam has a broader spectrum of activity than currently available β-lactamase inhibitors

β-lactamase class	Enzyme	Avibactam
Class A	TEM, SHV	✓
	CTX-M	✓
	KPC*	✓
Class B	NDM, VIM, IMP, VEB, PER	✗
Class C	AmpC	✓
	FOX	✓
	CMY-2	✓
	AAC-1	✓
Class D	OXA-48	✓

KPC, *Klebsiella pneumoniae* carbapenemases.
Adapted from: Lagacé-Wiens P, et al. Core Evid. 2014;9:13-25

Posology and method of administration

Type of infection	Dose ceftazidime–avibactam	Frequency	Infusion time	Duration of treatment
Complicated IAI	2 g/0.5 g	8 hours	2 hours	5–14 days
Complicated UTI, including pyelonephritis	2 g/0.5 g	8 hours	2 hours	5–10 days
Hospital-acquired pneumonia, including VAP	2 g/0.5 g	8 hours	2 hours	7–14 days
Infections due to aerobic Gram-negative organisms in patients with limited treatment options	2 g/0.5 g	8 hours	2 hours	Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress

IAI, invasive intra-abdominal infection; UTI, urinary tract infection; VAP, ventilator-associated pneumonia.

Special populations

Elderly

No dosage adjustment is considered necessary in elderly patients

Renal impairment

In patients with mild renal impairment (estimated creatinine clearance CrCL 51–≤ 80 mL/min) no dose adjustment is necessary

Dose recommendations are based on PK modelling

Following each haemodialysis, the dose of ceftazidime–avibactam recommended should be repeated and continued every 48 hours until next haemodialysis

Estimated CrCL (mL/min)	Dose regimen	Frequency	Infusion time
31–50	1 g/0.25 g	Every 8 hours	2 hours
16–30	0.75 g/0.1875 g	Every 12 hours	2 hours
6–15	0.75 g/0.1875 g	Every 24 hours	2 hours
ESRD including on haemodialysis	0.75 g/0.1875 g	Every 48 hours	2 hours

CrCL, creatinine clearance level; ESRD, end stage renal disease; PK, pharmacokinetics. Zavicefta SmPC. 2017.

Special populations

Hepatic impairment

No dosage adjustment is necessary in patients with hepatic impairment

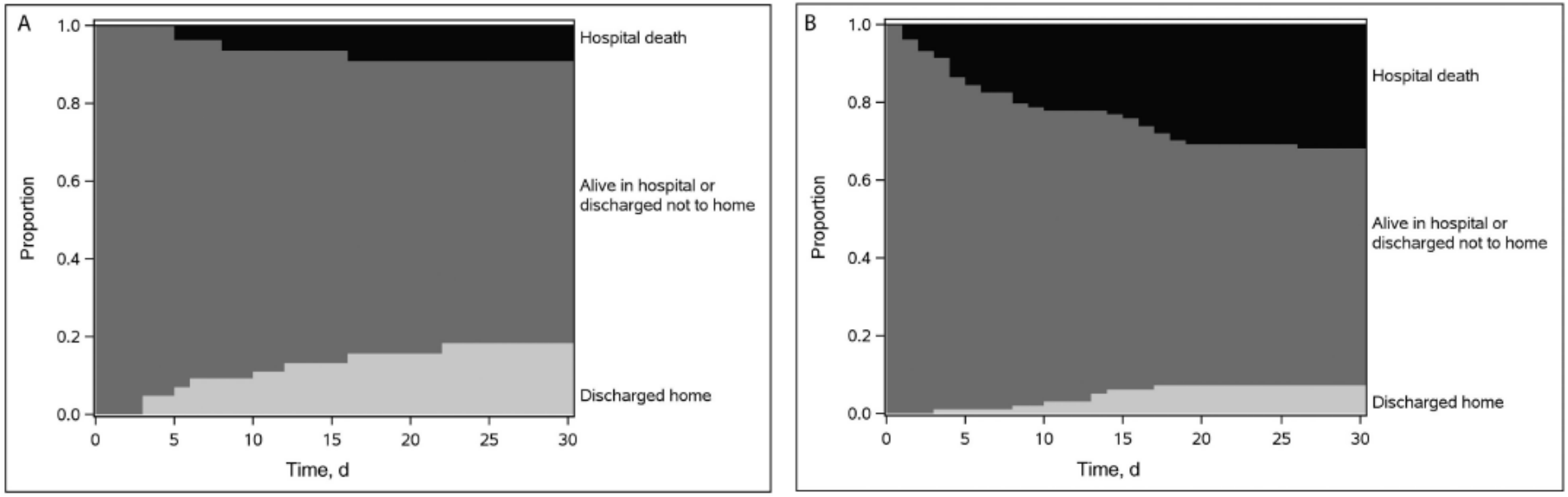
Paediatric population

Safety and efficacy in children and adolescents below 18 years of age have not yet been established

Zavicefta SmPC. 2017.

Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

- Inverse probability of treatment weighting (IPTW)–adjusted efficacy: disposition over time (n = 137; IPTW-adjusted probability estimates of hospital mortality and discharge status). *A,* Ceftazidime-avibactam group (n = 38). *B,* Colistin group (n = 99).



Van Duin, et al. Clinical Infectious Diseases® 2018;66(2):163–71

Colistin Versus Ceftazidime-Avibactam in the Treatment of Infections Due to Carbapenem-Resistant Enterobacteriaceae

Characteristic	Patients, No. (%)[a]			
	Ceftazidime-Avibactam (n = 38)	Colistin (n = 99)	All (N = 137)	*P* Value
Time to treatment, median (IQR), d[b]	3 (2–4)	2 (1–4)	3 (1–4)	.22[c]
Duration of treatment, median (IQR), d	10 (5–26)	10 (4–18)	10 (5–19)	.52[d]
Additional antibiotics				
None	14 (37)	6 (6)	20 (15)	<.001[e]
Tigecycline	12 (32)	60 (61)	72 (53)	.002[e]
Amikacin	6 (16)	23 (23)	29 (21)	.34[e]
Gentamicin	12 (32)	14 (14)	26 (19)	.02[e]
TMP/SMX	4 (11)	12 (12)	16 (12)	.80[e]
Carbapenem	11 (29)	59 (60)	70 (51)	.001[e]
Fosfomycin	1 (3)	3 (3)	4 (3)	>.99[c]

Van Duin, et al. Clinical Infectious Diseases® 2018;66(2):163–71

AGENZIA ITALIANA DEL FARMACO

DETERMINA 9 gennaio 2018

Classificazione del medicinale per uso umano «Zavicefta» ai sensi dell'art. 8, comma 10, della legge 24 dicembre 1993, n. 537. (Determina n. 10/2018). (18A00325)

(GU n.16 del 20-1-2018)

Confezione:

2000 mg/500 mg - polvere per concentrato per soluzione per infusione - uso endovenoso - flaconcino (vetro) - 10 flaconcini; A.I.C. n. 044931018/E (in base 10); classe di rimborsabilita': «H»; prezzo ex factory (IVA esclusa): € 1.108,03; prezzo al pubblico (IVA inclusa): € 1.828,69.

Sconto obbligatorio alle strutture pubbliche, ivi comprese le strutture di natura privato-convenzionata con il SSN, sul prezzo ex factory, come da condizioni negoziali.

Scheda di prescrizione cartacea, come da allegato 1) alla presente determinazione.

ALLEGATO

Scheda cartacea per la prescrizione della specialità medicinale ZAVICEFTA (ceftazidima/avibactam)

Indicazioni terapeutiche: Zavicefta è indicato per il trattamento delle seguenti infezioni negli adulti:

- infezione intra-addominale complicata (cIAI)
- infezione complicata del tratto urinario (cUTI), inclusa pielonefrite
- polmonite acquisita in ospedale (HAP), inclusa polmonite associata a ventilazione meccanica (VAP)

Zavicefta è inoltre indicato per il trattamento di infezioni causate da microrganismi Gram-negativi aerobi in pazienti adulti nei quali vi siano opzioni terapeutiche limitate.

La rimborsabilità è limitata al trattamento delle infezioni urinarie complicate (inclusa la pielonefrite) con documentata resistenza ad un trattamento di prima linea e al trattamento delle infezioni addominali complicate, delle polmoniti nosocomiali (inclusa la VAP), o di altre infezioni in pazienti con opzioni terapeutiche limitate, in cui vi sia sospetto o certezza di infezioni sostenute da batteri gram-negativi aerobi resistenti.

La prescrivibilità è riservata allo specialista infettivologo o, in sua assenza, ad altro specialista con competenza infettivologica ad hoc identificato dal Comitato Infezioni Ospedaliere (CIO)

con eziologia documentata/sospetta da batteri Gram-negativi, resistente ai trattamenti di prima linea	☐

PROGRAMMA TERAPEUTICO

Farmaco	Specialità	Dose	Durata prevista (cfr. RCP)
Zavicefta	2g./0,5g. polvere per concentrato per soluzione per infusione	2g. ceftazidima/0,5g. avibactam ogni 8 ore	

Il dosaggio standard in soggetti con CrCl>50 mL/min è 2 g. ceftazidima/0,5 g. avibactam ogni 8 ore (tempo di infusione: 2 h.) per una durata di 5-14 giorni nel trattamento delle cIAI, di 5-10 giorni nel trattamento delle cUTI (inclusa la pielonefrite acuta) e di 7-14 giorni per le polmoniti acquisite in ospedale (incluse le VAP). Vi è esperienza molto limitata per un utilizzo superiore a 14 giorni

Nome e cognome del Medico*: _____

Recapiti del Medico*: _____

** La prescrivibilità è riservata allo specialista infettivologo o, in sua assenza, ad altro specialista con competenza infettivologica ad hoc identificato dal Comitato Infezioni Ospedaliere (CIO) istituito per legge presso tutti i presidi ospedalieri (Circolare Ministero della Sanità n. 52/1985).*

TIMBRO E FIRMA DEL MEDICO RICHIEDENTE

Successive Emergence of Ceftazidime-Avibactam Resistance through Distinct Genomic Adaptations in bla_{KPC-2}-Harboring *Klebsiella pneumoniae* Sequence Type 307 Isolates

- While novel carbapenemase inhibitors fulfill an important need, they are unlikely to end the CRE epidemic.
- It remains to be determined if other carbapenemase inhibitors currently in trials will be equally vulnerable to the rapid evolution of resistance and which genetic backgrounds may be particularly problematic.
- This highlights the need to **optimize the use of current agents** to minimize the emergence of resistance and track the evolution of resistance with novel genomic tools, as well as the urgent need for novel treatments against MDR GNB infections.

Giddins MJ, et al. Antimicrob Agents Chemother 2018;62:e02101-17. https://doi.org/10.1128/AAC.02101-17

Accepted Manuscript Posted Online

AAC Accepted Manuscript Posted Online 14 May 2018
Antimicrob. Agents Chemother. doi:10.1128/AAC.00414-18
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Aztreonam-avibactam combination restores susceptibility of aztreonam in dual-carbapenemase-producing-*Enterobacteriaceae*

Ka Lip Chew[1]*, Michelle KL Tay[1], Bernadette Cheng[1], Raymond TP Lin[1,2], Sophie Octavia[2], Jeanette WP Teo[1]

[1] National University Hospital, Department of Laboratory Medicine, Singapore

[2] National Public Health Laboratory, Ministry of Health, Singapore

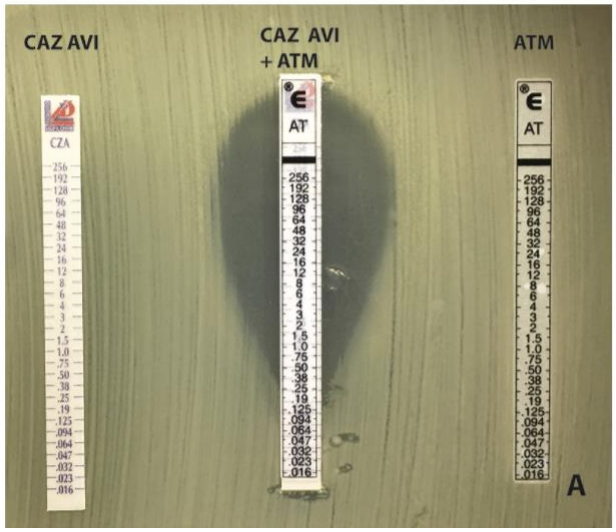
Table 1: Susceptibility of CPE carrying dual carbapenemases to aztreonam and avibactam singly, and in combination

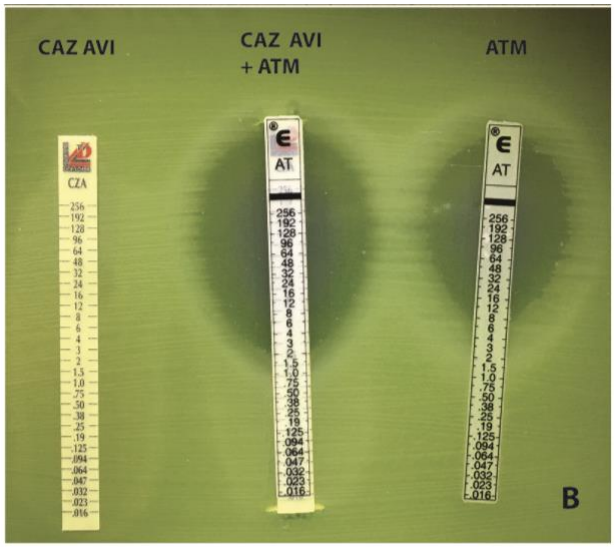
Carbapenemase genes	Avibactam (mg/L)			Aztreonam (mg/L)			Aztreonam/avibactam*(mg/L)		
	MIC range	MIC_{50}	MIC_{90}	MIC range	MIC_{50}	MIC_{90}	MIC or MIC range	MIC_{50}	MIC_{90}
NDM-1 + IMP-4 (1 *K. pneumoniae*)	>64	-	-	32	-	-	0.25	-	-
NDM + KPC-2 (11 *K. pneumoniae*, 2 *E. cloacae* complex, 1 *C. freundii*)	16 — >64	64	>64	32 — >64	64	>64	≤0.06 — 4	0.12	1
NDM + OXA-48-like (32 *K. pneumoniae*, 13 *E. coli*, 4 *E. cloacae* complex, 6 *C.freundii*)	4 — >64	32	>64	32 — >64	>64	>64	≤0.06 — 8	0.5	4
All isolates (n = 70)	4 — >64	64	>64	32 — >64	>64	>64	≤0.06 — 8	0.5	2

*Avibactam constant concentration of 4mg/L

Ka Lip Chew, et al. Antimicrob. Agents Chemother. 2018 doi:10.1128/AAC.00414-18

Ceftazidime-Avibactam and Aztreonam, an Interesting Strategy To Overcome $\mathcal{B}$-Lactam Resistance Conferred by Metallo- $\mathcal{B}$-Lactamases in *Enterobacteriaceae* and *Pseudomonas aeruginosa*





Susceptibility testing showing with ellipsometry the effect of the synergistic combination of CAZ-AVI and ATM. The combination (middle strip) was tested by first applying an ATM strip to the Mueller-Hinton (MH) agar, removing it after 5 min, and then applying a CAZ-AVI strip on the exact same location and placing back the ATM strip to read the susceptibility to ATM in the presence of AVI (and CAZ). (Left panel) *K. pneumoniae* NDM-1/OXA-48 from patient 1. (Right panel) *Pseudomonas aeruginosa* NDM-1/AmpC from patient 2.

Davido B, et al. AAC 61:e01008-17. https://doi.org/10.1128/AAC .01008-17.

Imipenem-relebactam

- Relebactam is a non-β-lactam serine β-lactamase inhibitor, similar to avibactam, that was designed to have inhibitory activity against class A and C β-lactamases.
- In vitro assays with CRE isolates demonstrated that MICs were significantly lowered when imipenem was tested with relebactam against KPC-producing K. pneumoniae (MIC50 = 0.25/4 mg/mL; MIC90 = 1/4 mg/mL).
- Compared to imipenem alone, little reduction in imipenem-relebactam MICs were noted in OXA-48-producing K. pneumoniae or OXA-23-producing A. baumannii, suggesting that that **relebactam,**

Phase 3 Clinical Program of Relebactam/Imipenem/Cilastatin Ongoing

- Two pivotal Phase 3 clinical studies of relebactam in combination with imipenem/cilastatin are currently ongoing and recruiting patients.
- One study compares treatment with imipenem/relebactam, as a fixed-dose combination, with piperacillin/tazobactam in patients with **hospital-acquired bacterial pneumonia or ventilator-associated bacterial pneumonia**. The primary hypothesis of this study is that imipenem/relebactam is non-inferior to piperacillin/tazobactam in the incidence rate of all-cause mortality. (www.ClinicalTrials.gov Identifier: NCT02493764)
- A second study evaluates the efficacy and safety of imipenem/relebactam versus colistimethate sodium in combination with imipenem in the **treatment of imipenem-resistant bacterial infections, including those caused by *Pseudomonas aeruginosa* and KPC-producing organisms**. Infections evaluated in this study include hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, complicated intra-abdominal infections and complicated urinary tract infections. (www.ClinicalTrials.gov Identifier: NCT02452047)

Meropenem-vaborbactam (formerly known as RPX7009)

- Vaborbactam (VAB; formerly RPX7009) is a novel beta-lactamase inhibitor based on a cyclic boronic acid pharmacophore with potent inhibitory activity against Ambler class A and C beta-lactamases.
- It has been co-formulated with meropenem to restore its activity against *Klebsiella pneumoniae* carbapenemases (KPC).
- VAB does not inhibit class B or D carbapenemases, nor does it improve the activity of meropenem against multidrug-resistant nonfermenting gram-negative bacilli, notably

The Medicines Company Announces FDA Approval of VABOMERE™ (meropenem and vaborbactam)

30 Aug 2017

–Accelerated approval for the treatment of adult patients with complicated urinary tract infections, including pyelonephritis–

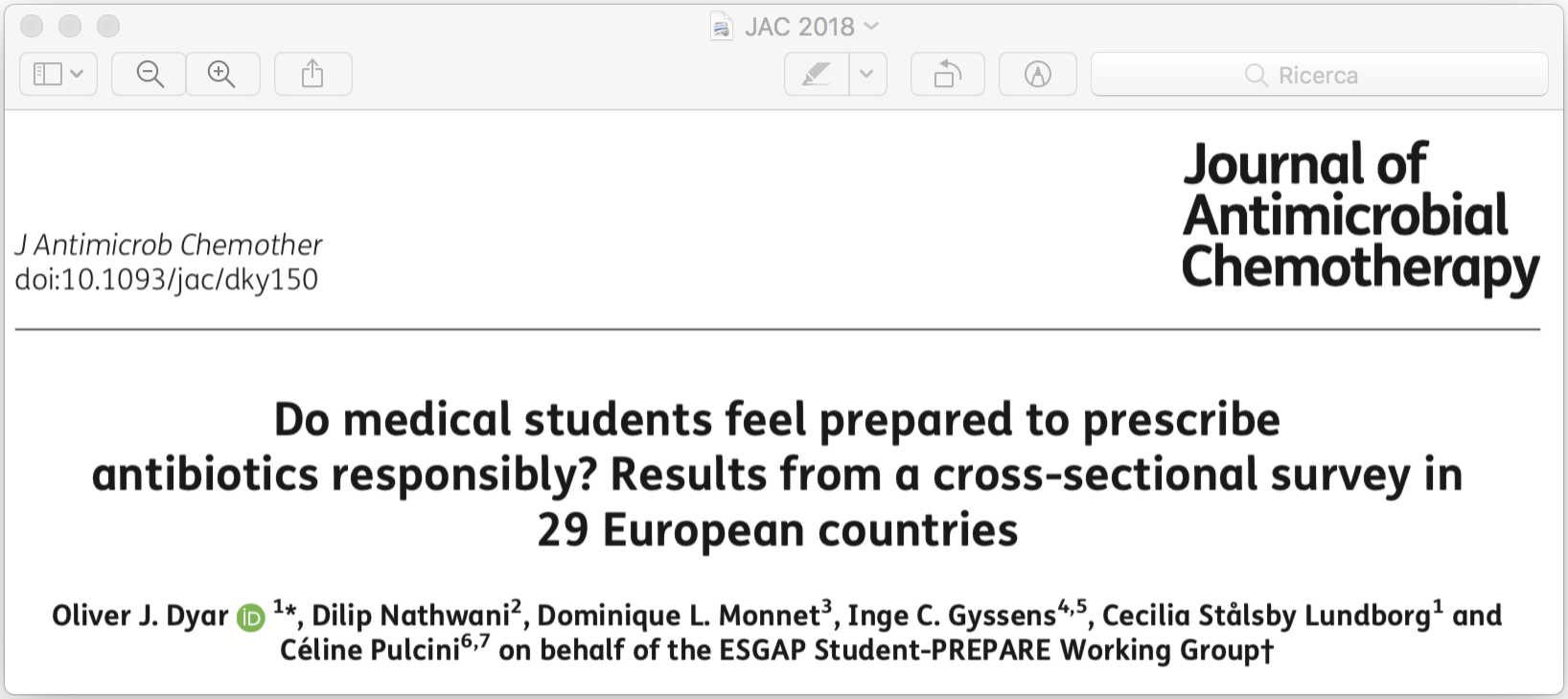
–First carbapenem-based combination product – combination of meropenem with a new class of beta-lactamase inhibitor –

–Addresses pathogens designated by the CDC as urgent and serious antimicrobial resistance threats, and pathogens cited by the WHO as a critical need for new antibiotics–

–VABOMERE expected to be available in the fourth quarter of 2017–

Summary on the novel β-lactamase inhibitors

- A few novel β-lactamase inhibitors are currently in development
- Ceftolozane-Tazobactam has strong activity agaisnts ESBL enterobacteriaceae and is the most active agent against *Pseudomonas aeruginosa*
- Ceftazidime–avibactam is the first of these new agents to be licensed in Europe with a wide spectrum of activity including ESBLs, AmpC, KPC and OXA-48
- Other β-lactam/β-lactamase inhibitor combinations in development are targeting additional β-lactamases including class B metallo-enzymes



JAC 2018

Ricerca

J Antimicrob Chemother
doi:10.1093/jac/dky150

Journal of Antimicrobial Chemotherapy

Do medical students feel prepared to prescribe antibiotics responsibly? Results from a cross-sectional survey in 29 European countries

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- **Conclusions:** Most final-year European medical students feel they still need **more education on antibiotic use for their future practice** as junior doctors. Patterns of preparedness on specific topics were identified, were highly consistent across countries, and correlated with both perceived need for further education and levels of antibiotic resistance among common bacteria.

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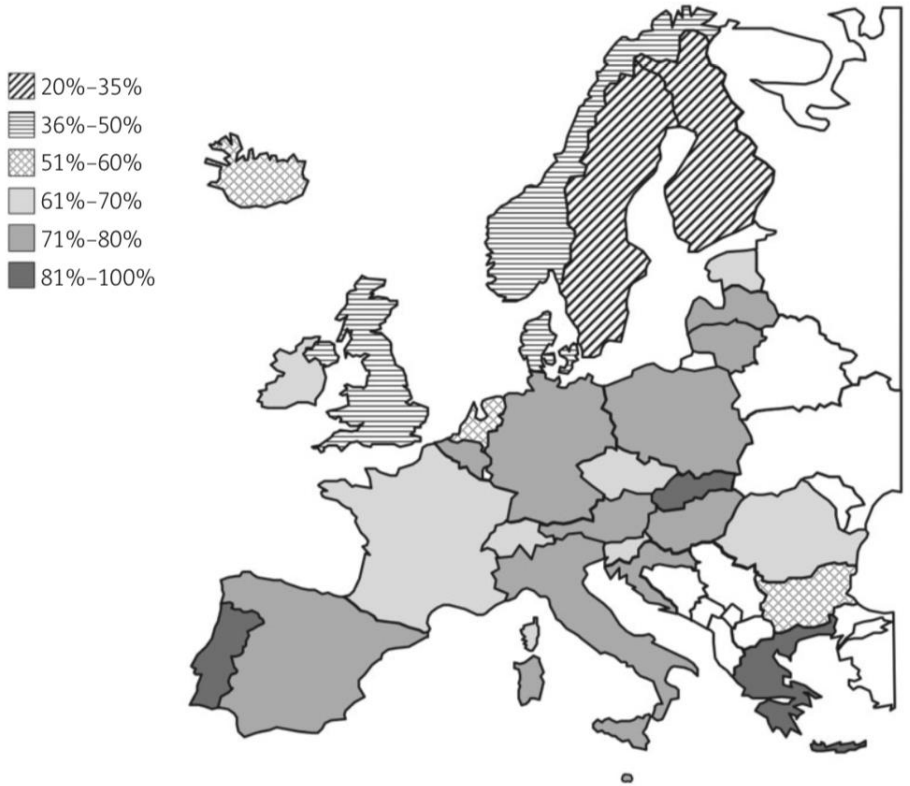

Figure 1. Percentage of European medical students who feel they need more education on antibiotic use, illustrated by country, 2015. The figure is based on responses from 7044 students and presents results aggregated first at medical school level within a country, then at country level.