Θεραπεία Πολυανθεκτικών Gram-αρνητικών Μικροβίων

Γεώργιος Λ. Δαΐκος

Καθηγητής Παθολογίας Λοιμώξεων, Ιατρική Σχολή ΕΚΠΑ

An international expert proposal for interim standard definitions for acquired resistance

Magiorakos AP et al. CMI 2012; 18: 268–281.

Definitions

- MDR: resistant to ≥3 antibiotic classes
- XDR: resistant to all but two classes, such as polymyxins and glycylcyclines),
- PDR: resistant to all commercially available antibiotics

Consequences

- Cause serious infections associated with increased morbidity and mortality
- Prolong hospital stay and increase cost
- Limited treatment options

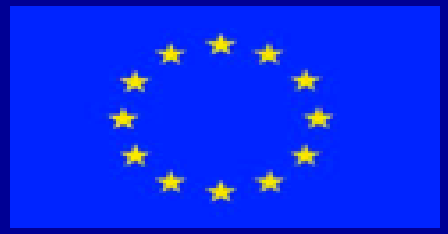
Estimates of Burden of Antibacterial Resistance

European Union
population 500m

25,000 deaths per year

2.5m extra hospital days

Overall societal costs
(€ 900 million, hosp. days)
Approx. €1.5 billion per year



Source: ECDC 2007

Thailand
population 70m

>38,000 deaths

>3.2m hospital days

Overall societal costs
US$ 84.6–202.8 mill. direct
>US$1.3 billion indirect

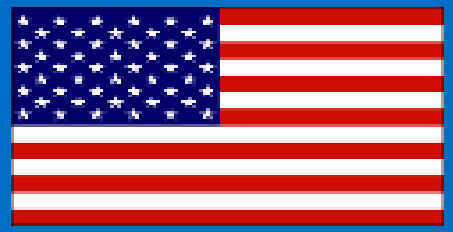
Source: Pumart et al 2012

United States
population 300m

>23,000 deaths

>2.0m illnesses

Overall societal costs
Up to $20 billion direct
Up to $35 billion indirect

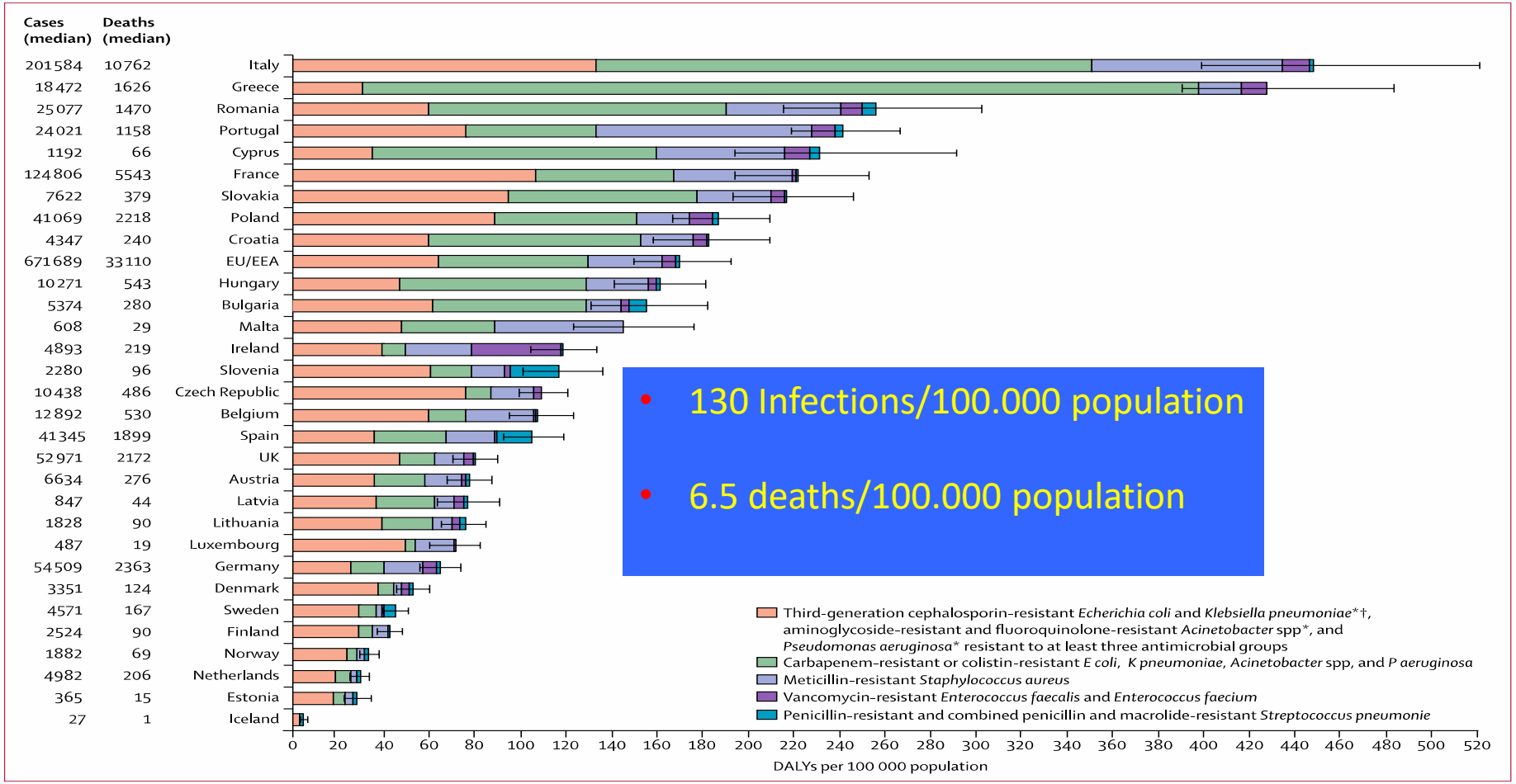


Source: US CDC 2013

Global information is insufficient to show complete disease burden impact and costs

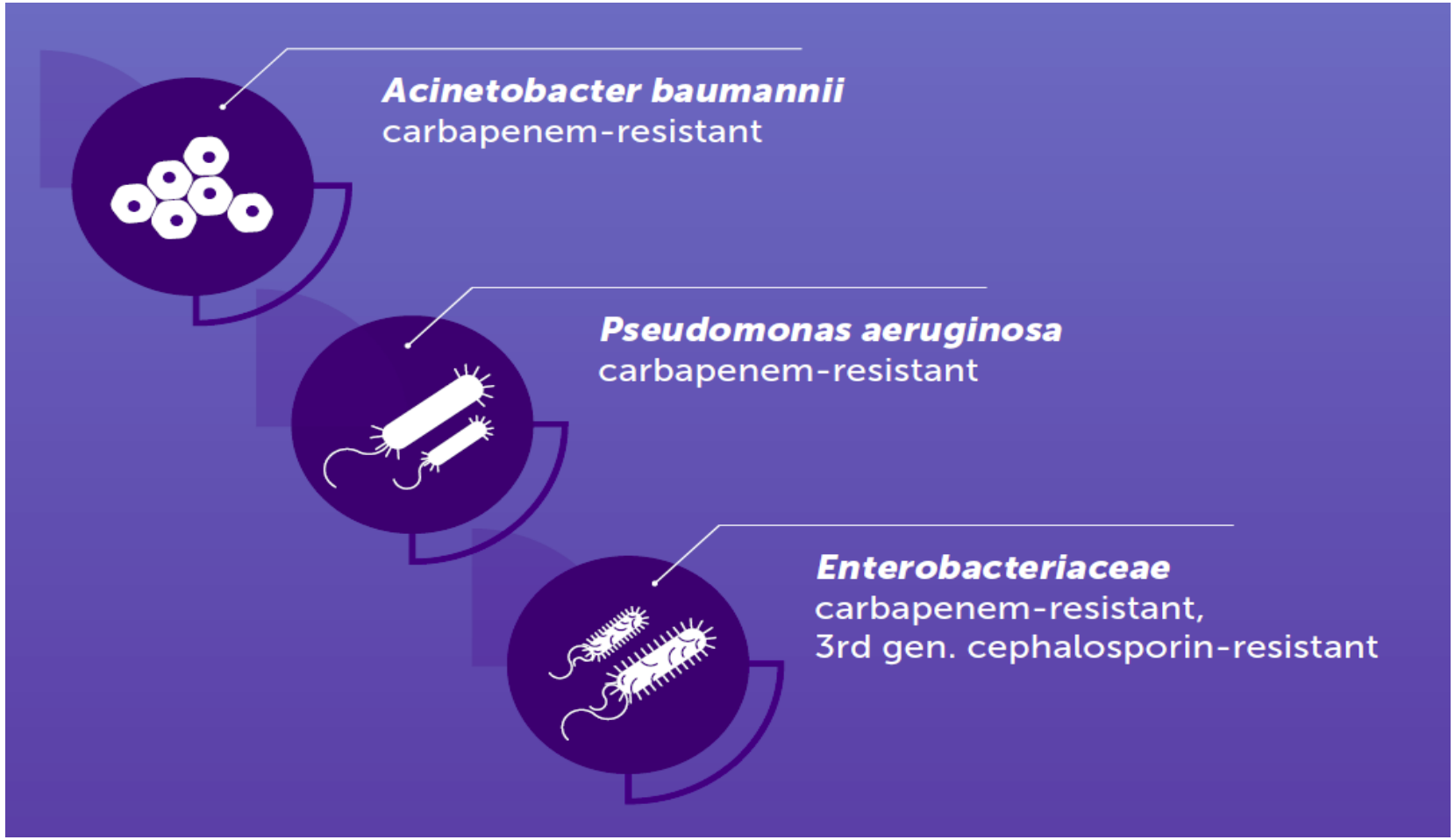
Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis

Alessandro Cassini, Liselotte Diaz Högberg, Diamantis Plachouras, Annalisa Quattrocchi, Ana Hoxha, Gunnar Skov Simonsen, Mélanie Colomb-Cotinat, Mirjam E Kretzschmar, Brecht Devleesschauwer, Michele Cecchini, Driss Ait Ouakrim, Tiago Cravo Oliveira,

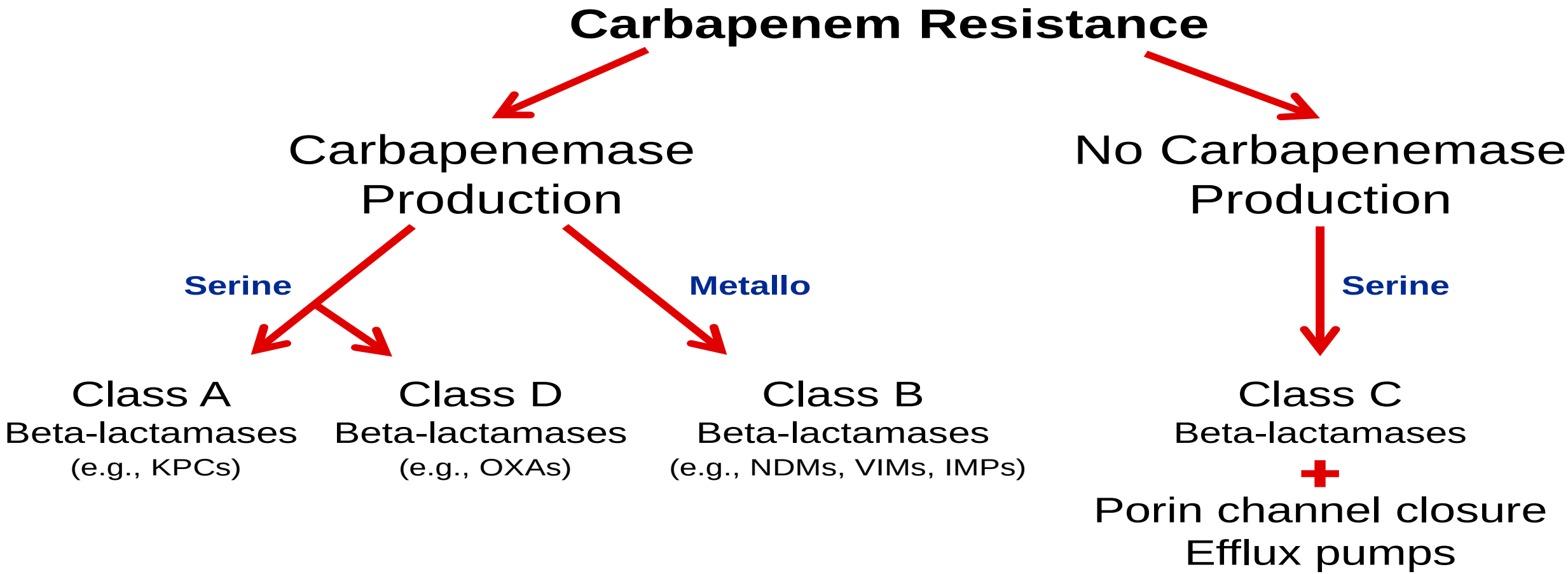


Cassini A Lancet ID DOI: 10.1016/S1473-3099(18)30605-4

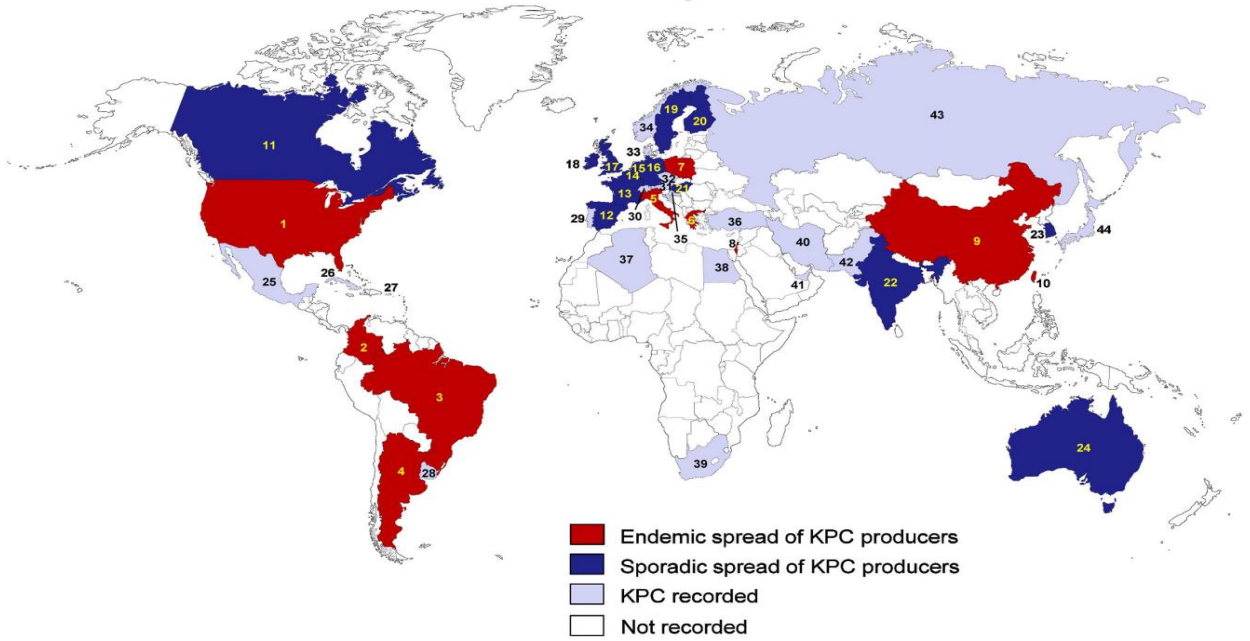
WHO priority pathogens list “Critical priority”



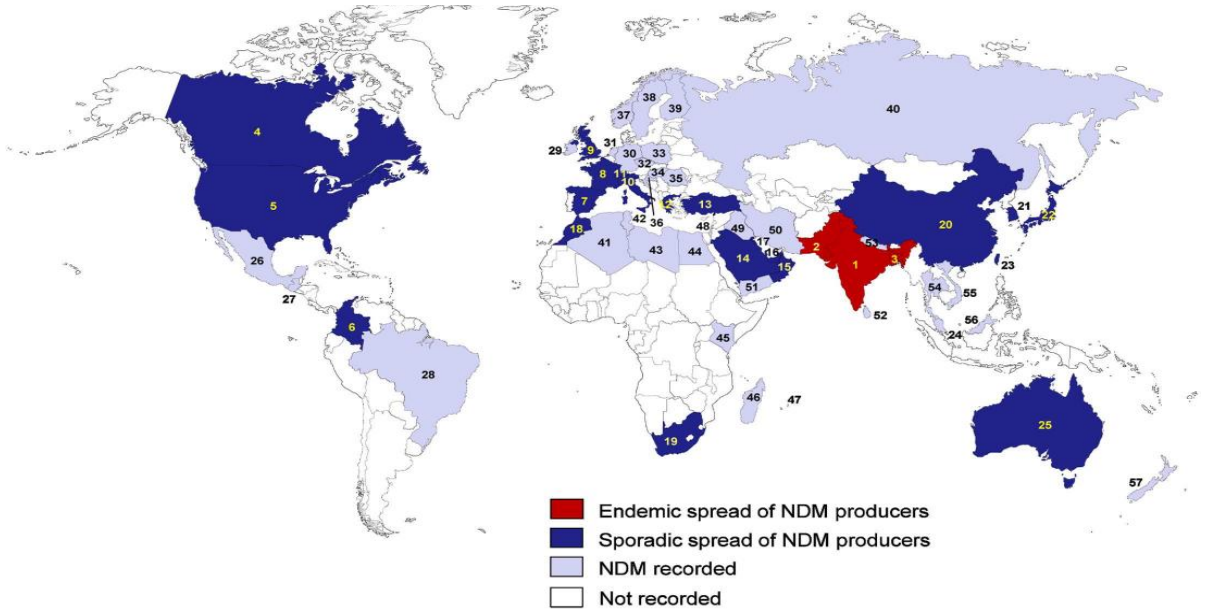
Geneva: World Health Organization; 2017(WHO/EMP/IAU/2017.12).


Carbapenem Resistance
Carbapenemase Production
No Carbapenemase Production
Serine
Metallo
Serine
Class A
Beta-lactamases
(e.g., KPCs)
Class D
Beta-lactamases
(e.g., OXAs)
Class B
Beta-lactamases
(e.g., NDMs, VIMs, IMPs)
Class C
Beta-lactamases
+
Porin channel closure
Efflux pumps

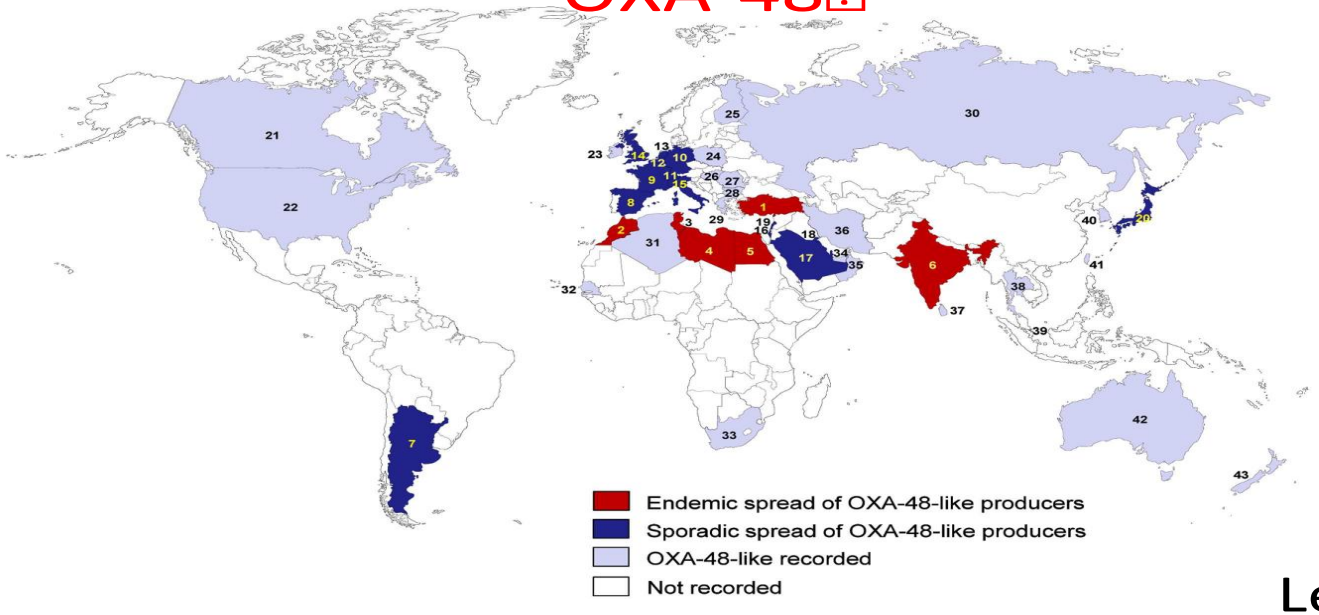
KPC



NDM



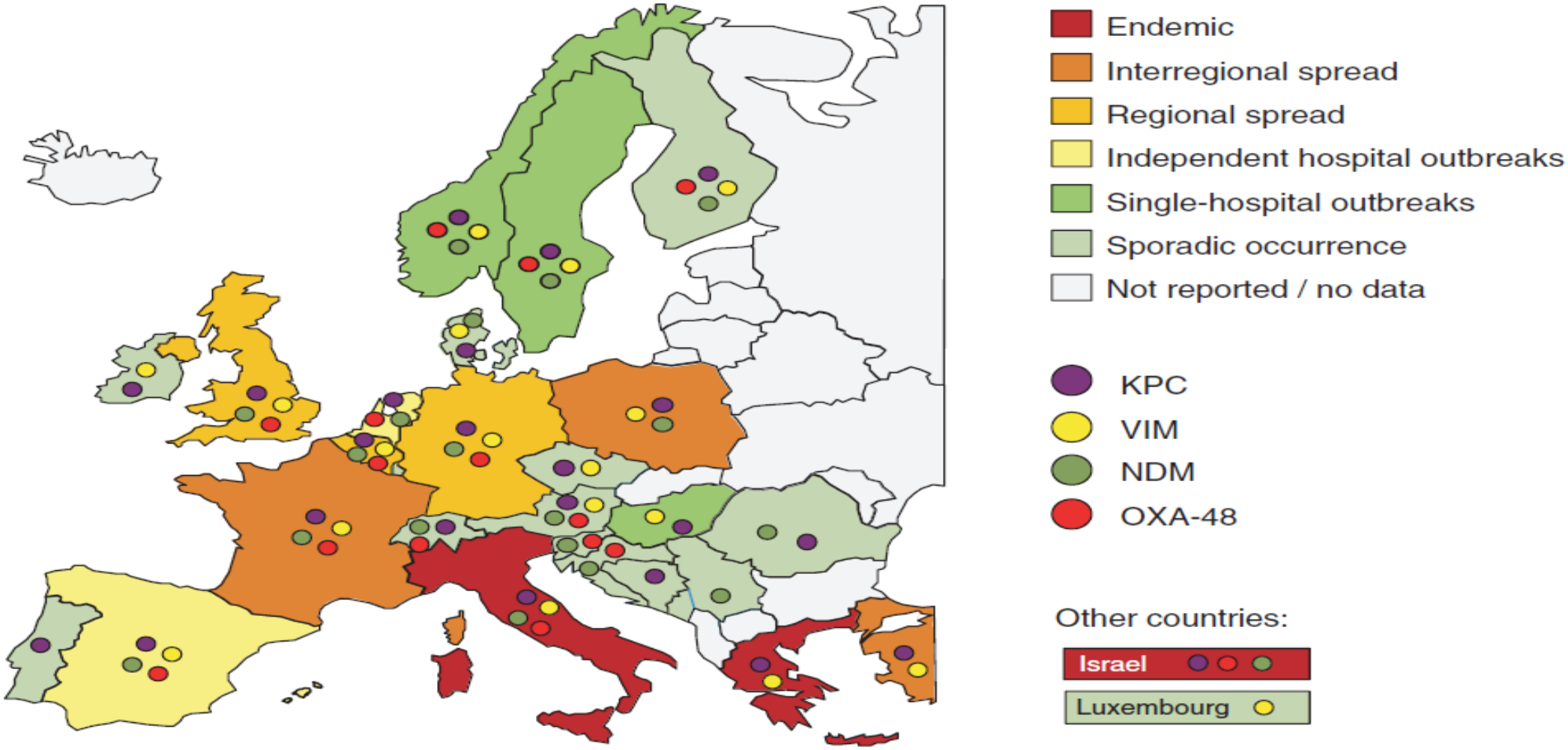
OXA-48



The VIM and IMP producing strains are largely confined to their original foci i.e. the Mediterranean countries (VIM) and the Far East (IMP)

Lee CR Fron J ers In Microbiol 2016; 7: 895

Distribution of Carbapenemases in Europe



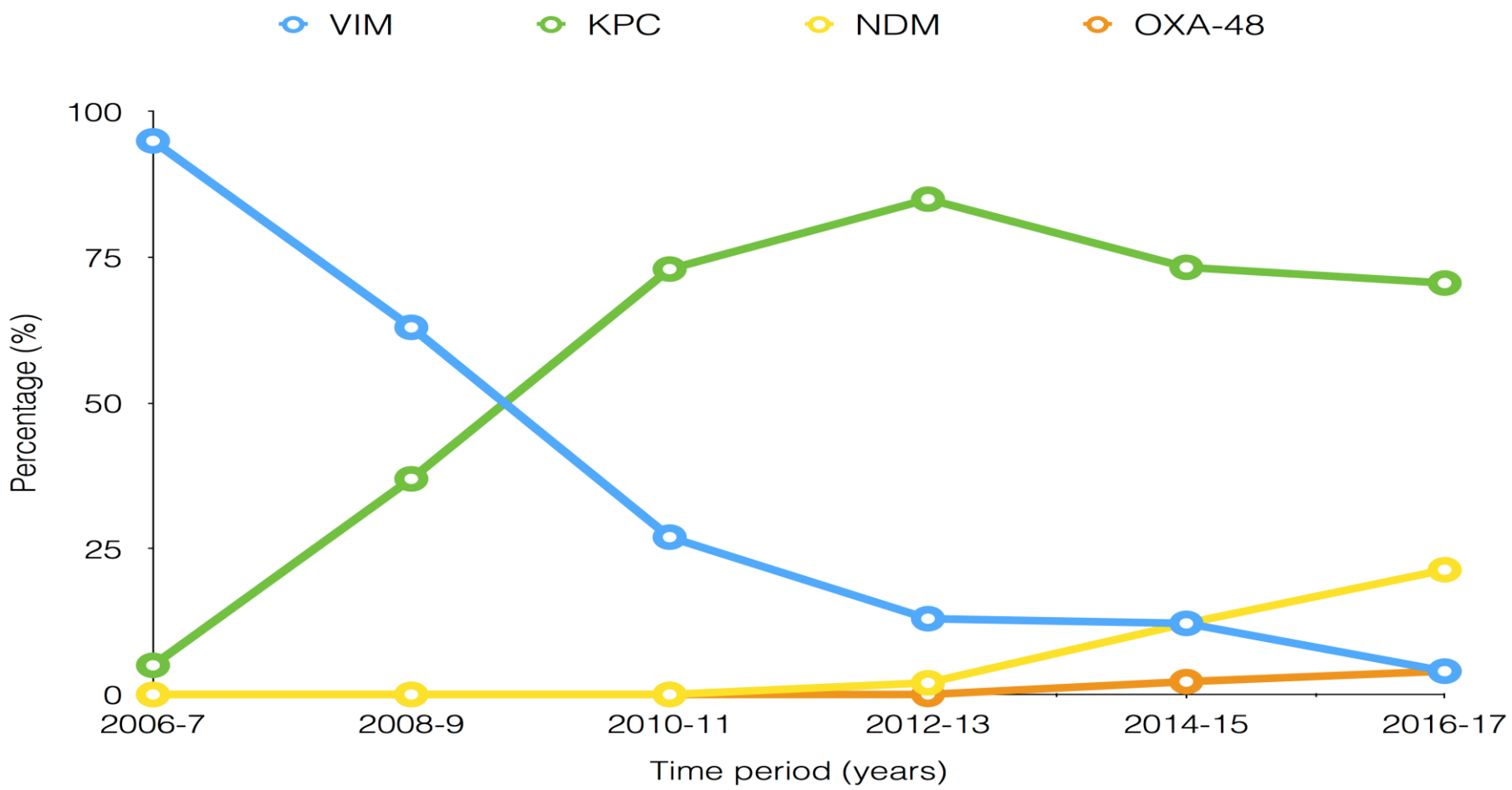
R Canton Clin Microbiol Infect 2012; 18: 413–431

HIGH RISK MDR CLONES WITH GLOBAL SPREAD

High-risk clone	Geographic distribution	Predominant resistance mechanism[a]	Extent of resistance[b]
Escherichia coli			
ST131	Global	CTX-M-15	MDR
Klebseilla pneumoniae			
ST258	Global	KPC-2, KPC-3	XDR, PDR
ST11	South America, East Asia, South Asia, Europe	KPC-2, NDM-1, VIM, OXA-48	XDR, PDR
ST340	West Asia, North America, Europe	NDM, KPC, KPC-2, NDM-1	XDR, PDR
ST512	Europe, West Asia	KPC-3	XDR, PDR
ST147	North America, Europe, East Asia, West Asia, South Asia	KPC, KPC-2, NDM-1, OXA-48, OXA-48-like, VIM	XDR, PDR
ST15	North America, Europe	OXA-48	XDR, PDR
Acinetobacter baumannii			
ICLI	Global	NDM, OXA-23, OXA-58, VIM	XDR, PDR
CC1/CC109			
ICLII	Global	NDM, OXA-23, OXA-24/40, OXA-58, VIM	XDR, PDR
CC2/CC92			
Pseudomanas aeruginosa			
ST235	Europe, Asia, South America, Africa	IMP, VIM	XDR, PDR
ST111	Europe	IMP, VIM,	XDR, PDR

Data extracted from Diene and Rolain CMI 2014; 20: 831

Prevalence of CP-KP by Type of Carbapenemase (2006-2017-Laiko General Hospital)



CP-KP: Carbapenemase producing *Klebsiella pneumoniae*

G. Daikos, Personal Data

Current Trends in Epidemiology of CPEs

Hospital setting

- Predominant bacterial host
  - *K. pneumoniae*
- Predominant enzymes
  - KPC
  - VIM
  - NDM
  - OXA-48

Community setting

- Predominant bacterial host
  - *E. coli*
- Predominant enzymes
  - NDM
  - OXA-48

EID 2014; 20:1170

RESEARCH

Deaths Attributable to Carbapenem-Resistant *Enterobacteriaceae* Infections

Matthew E. Falagas,[1] Giannoula S. Tansarli,[1] Drosos E. Karageorgopoulos,[1] and Konstantinos Z. Vardakas[1]

- Pooled analysis of the 9 studies (985 patients) showed
- Death rate of CRE-infected > CSE-infected patients
- RR 2.05, 95% CI 1.56–2.69

Therapeutic Options for CR-GNB Infections

Pseudomonas

- Colistin
- Fosfomycin
- Aztreonam?
- Ceftolozane/tazobactam
- Ceftazidime/avibactam

Klebsiella

- Colistin
- Aminoglycosides
- Tigecycline
- Fosfomycin
- Aztreonam?
- Carbapenems?
- Ceftazidime/avibactam

Acinetobacter

- Colistin
- Tigecycline
- Sulbactam
- Trimethoprim/sulfamethoxazol
- Minocycline

Therapeutic Optios for CRE Infections

Available Agents

- Polymyxins
- Aminoglycosides
- Tigecycline
- Fosfomycin
- Aztreonam?
- Carbapenems?

Newer Agents

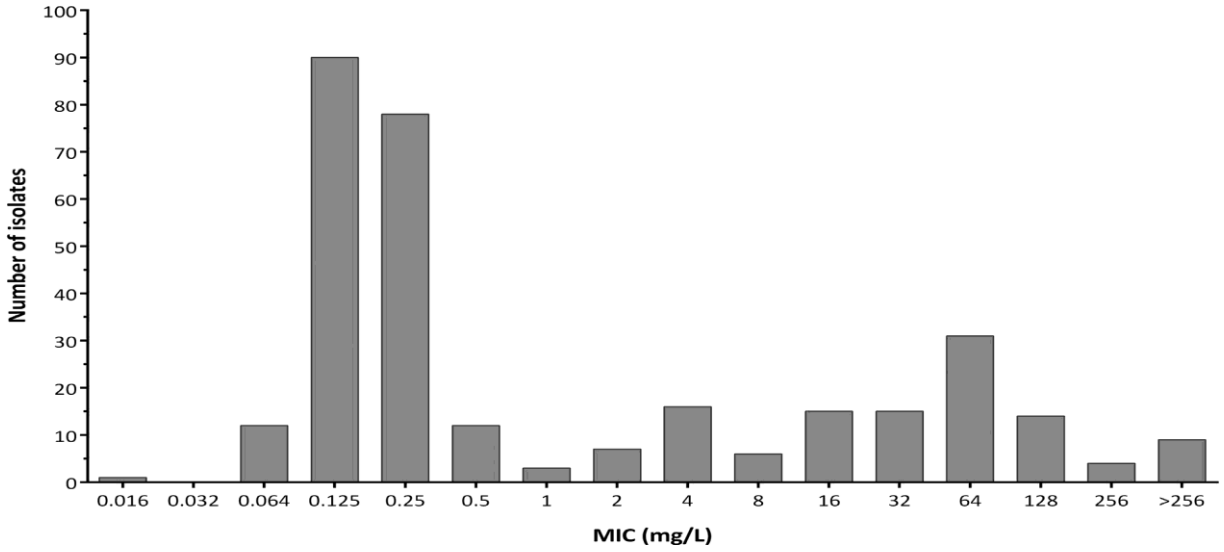
- Meropenem-vaborbactam
- Imipenem/relebactam
- Plazomicin
- Eravacycline
- Cefiderocol
- Aztreonam-avibactam

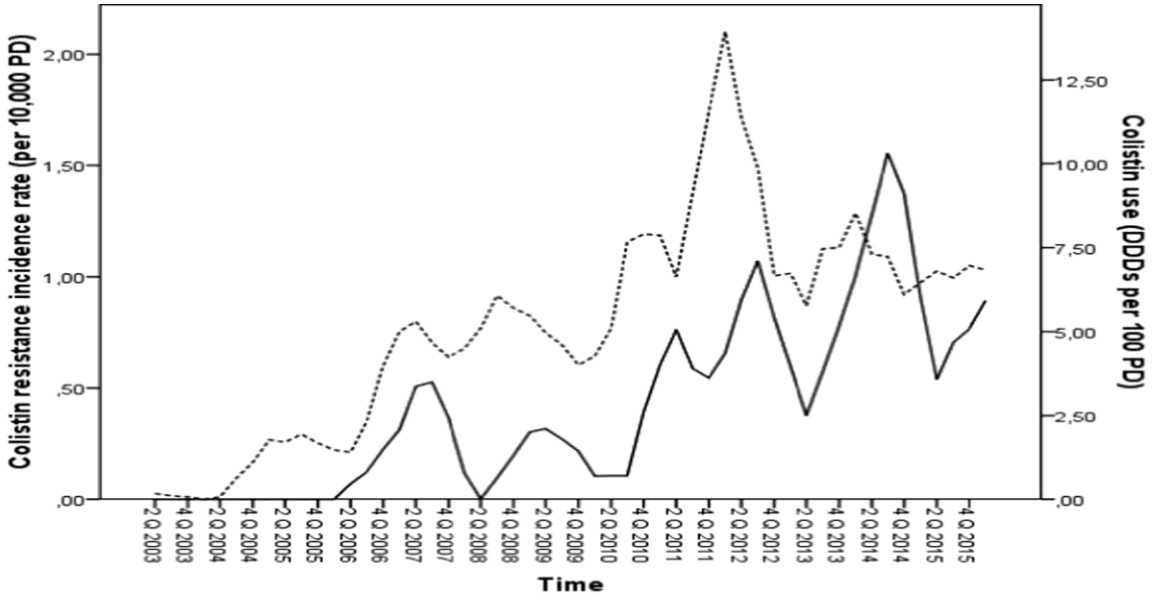
Colistin resistance superimposed to endemic carbapenem-resistant *Klebsiella pneumoniae*: a rapidly evolving problem in Italy, November 2013 to April 2014

M. Monaco[1,2], T Giani[2,3], M Raffone[1,4], F Arena[3], A Garcia-Fernandez[1], S Pollini[3], Network EuSCAPE-Italy[5], H Grundmann[6], A Pantosti (annalisa.pantosti@iss.it)[1], G M Rossolini[3,7,8]

Antimicrobial agent	No. of KPC-KP (% non-susceptible)
Colistin	**76 (43)**
Gentamicin	29 (16)
Tigecycline	11 (6)

Evolution of Colistin Resistance among CP-Kp Laiko Hospital 2003-2015





Tansarli G IJAA 2018; 52: 397–403

Response to Treatment

- Host
- Infection (site and severity)
- Bacteria
- Treatment regimens

ORIGINAL ARTICLE

MAYO CLINIC

A Predictive Model of Mortality in Patients With Bloodstream Infections due to Carbapenemase-Producing Enterobacteriaceae

TABLE 3. Assignment of Scores on the Basis of the Regression Coefficients Obtained for the Selected Variables Using Hierarchical Logistic Regression

Variable	Regression coefficient (95% CI)	Score
Severe sepsis or septic shock	1.76 (1.01-2.50)	5
Pitt score ≥6	1.39 (0.54-2.25)	4
Charlson comorbidity index ≥2	0.93 (0.09-1.78)	3
Source of BSI other than urinary or biliary tract	0.92 (0-1.85)	3
Inappropriate early targeted therapy	0.69 (0.07-1.31)	2
Total points		*17*

BSI = bloodstream infection.

Validation for any type of KPC Infection

- Score < 8, mortality 21.3%
- Score ≥ 8 , mortality 73.1%

AUROC: 0.78 (95% CI 0.65–0.91)

Belén Gutiérrez-Gutiérrez
Mayo Clin Proc. 2016; 91: 1362

Cano A CID 2018; 66: 1204

J Antimicrob Chemother 2014; **69**: 2305–2309
doi:10.1093/jac/dku168 Advance Access publication 28 May 2014

Journal of Antimicrobial Chemotherapy

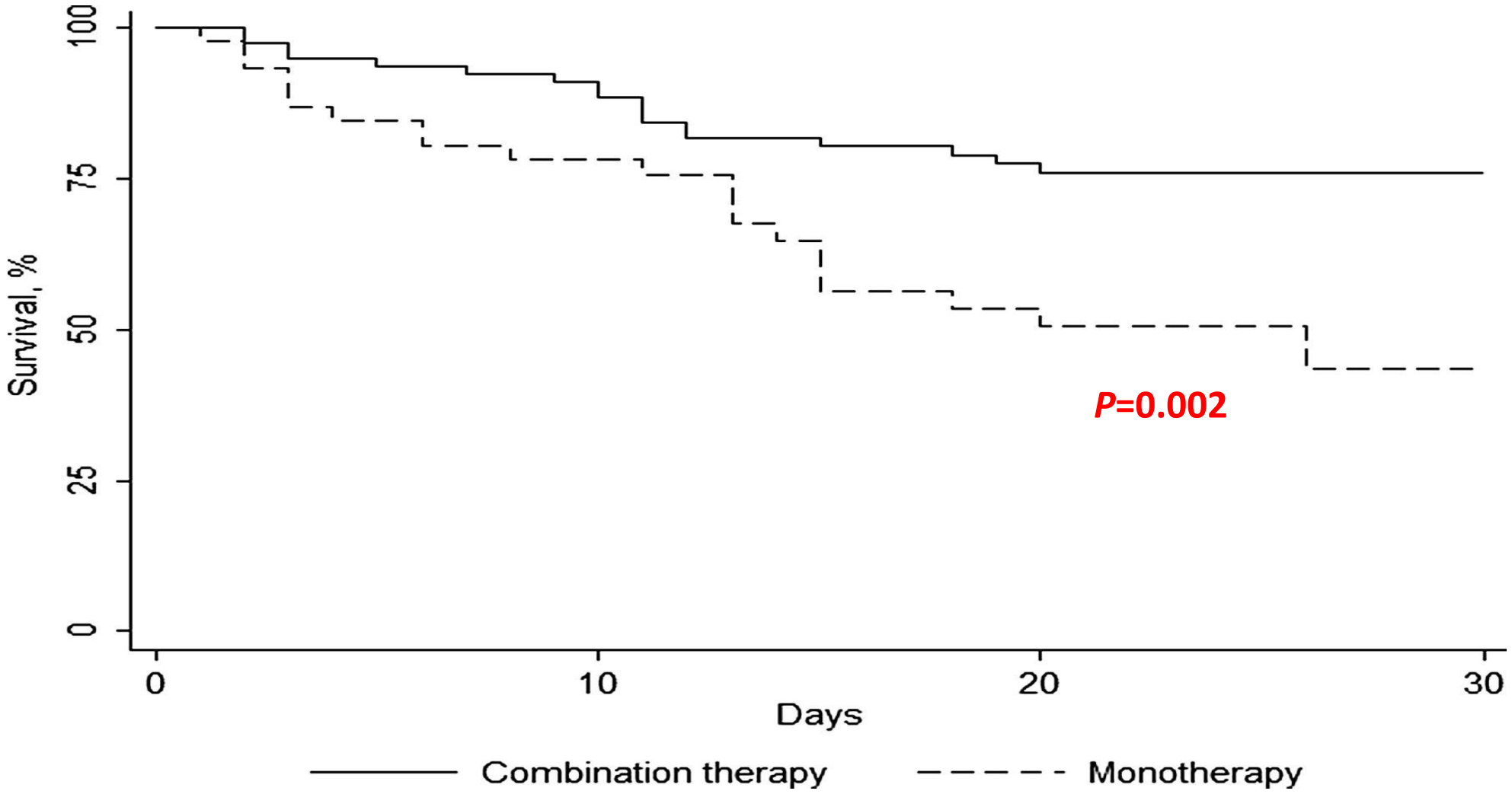
Combination therapy for carbapenem-resistant Gram-negative bacteria

Mical Paul[1]*, Yehuda Carmeli[2], Emanuele Durante-Mangoni[3], Johan W. Mouton[4], Evelina Tacconelli[5], Ursula Theuretzbacher[6], Cristina Mussini[7] and Leonard Leibovici[8,9]

- Few randomized control trials and all underpowered
- Observational studies
  - Small study size, selection bias
  - Different outcome definitions
  - Different definitions of combination therapy
  - Different breakpoints (EUCAST, CLSI, old, new
  - Many treatment regimens

The quality of evidence supporting the management of CRE infections remains low

Kaplan Meier Curves of Survival Propability of Patients with KPC BSIs According to Treatment



Tumbarello M et al. Clin Infect Dis. 2012;55:943-950

AAC
Journals.ASM.org

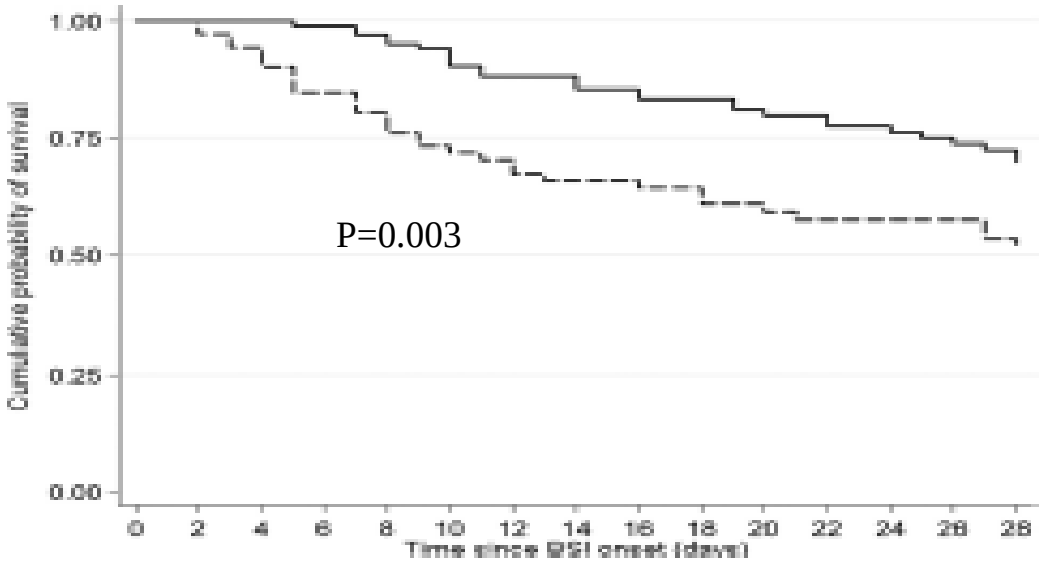
Carbapenemase-Producing *Klebsiella pneumoniae* Bloodstream Infections: Lowering Mortality by Antibiotic Combination Schemes and the Role of Carbapenems

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]

2014

205 patients with CP Kp bacteremia

Treatment with a combination: Independent predictor of survival!!

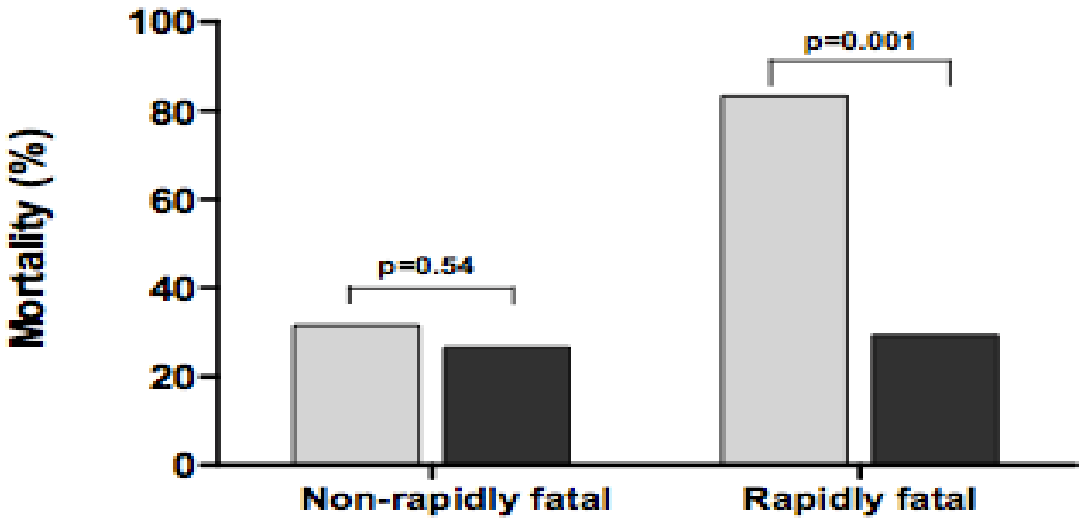


	Mortality %
No active drug	33.3
Monotherapy	44.4
Combination	27.2
without a carbapenem	30.6
with a carbapenem	19.3

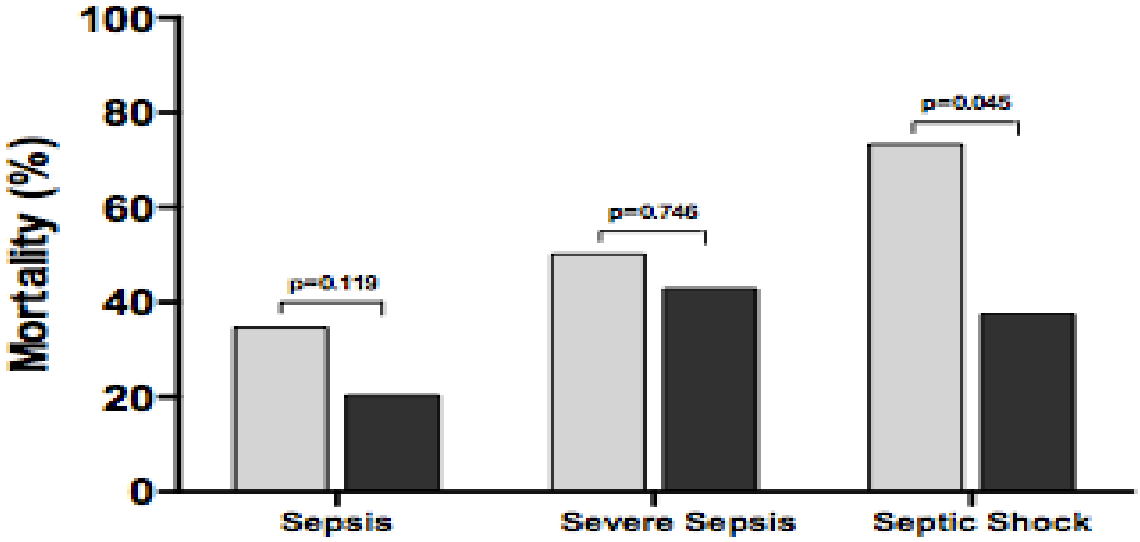
***P* 0.018**

Effect of treatment against CP-Kp BSIs
(monotherapy vs combination therapy)

By severity of underlying disease

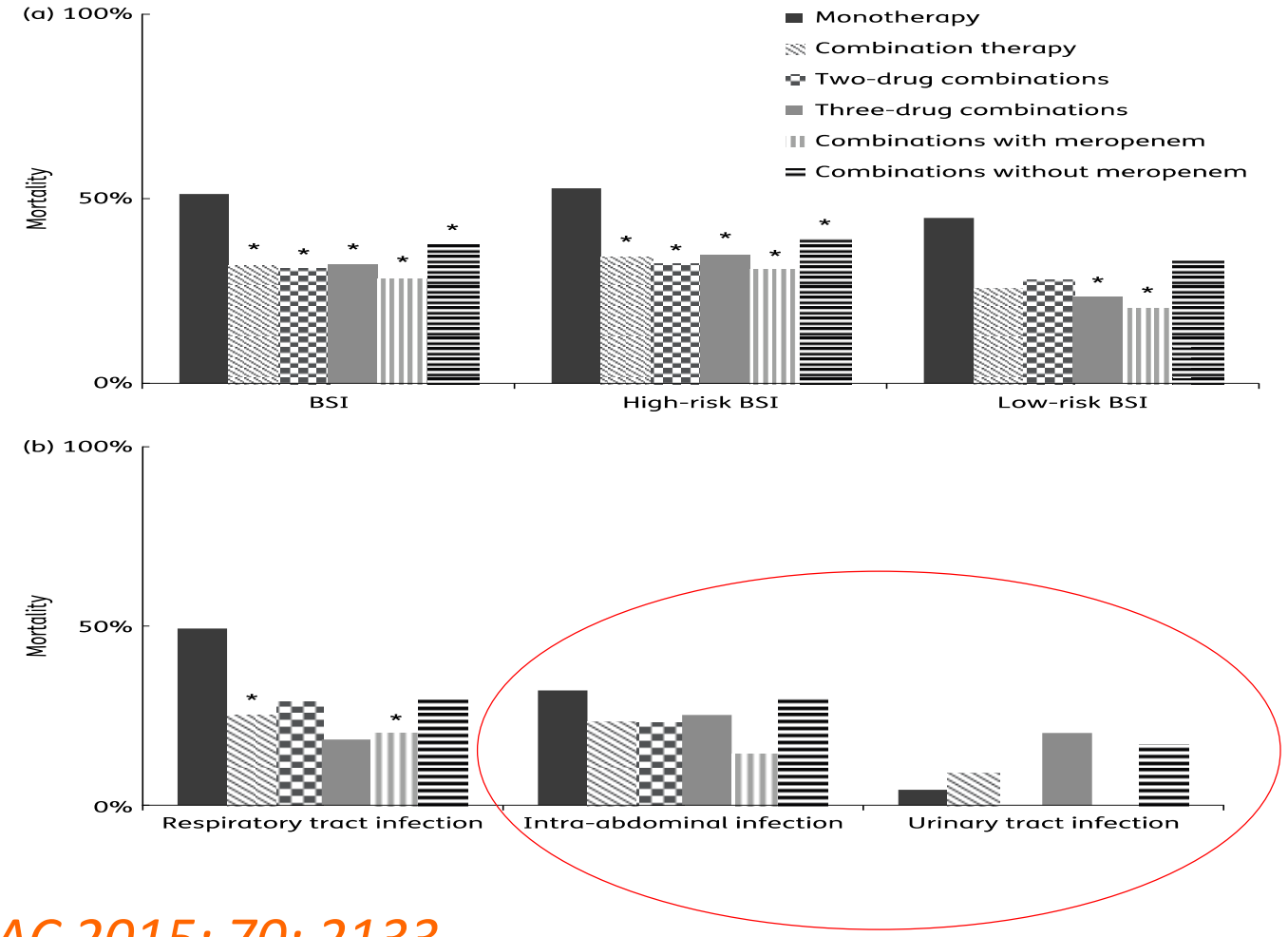


By severity of sepsis



Daikos GL AAC 2014; 58: 2322

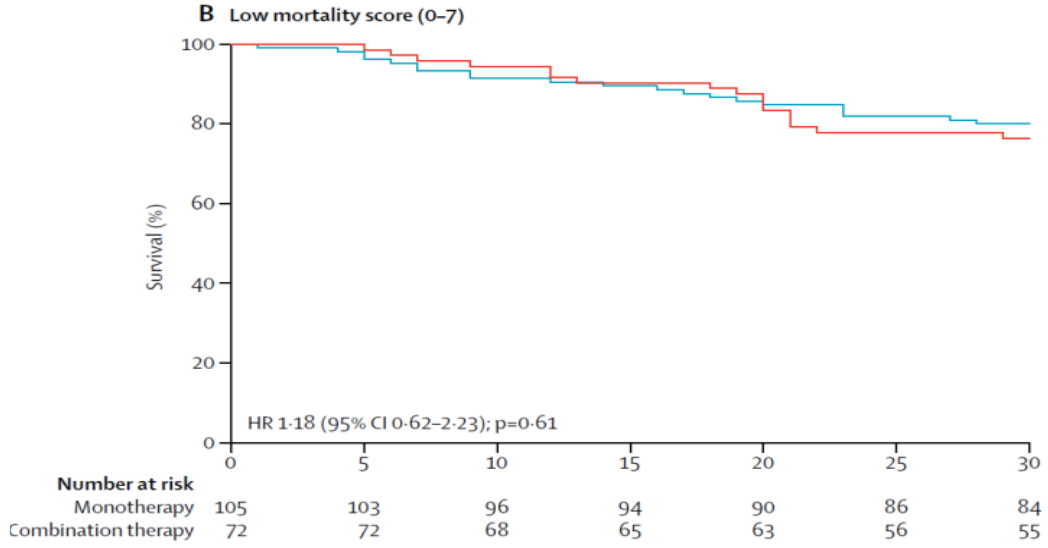
Mortality rates associated with different antimicrobial drug regimen categories in patients with BSIs or non-bacteraemic infections



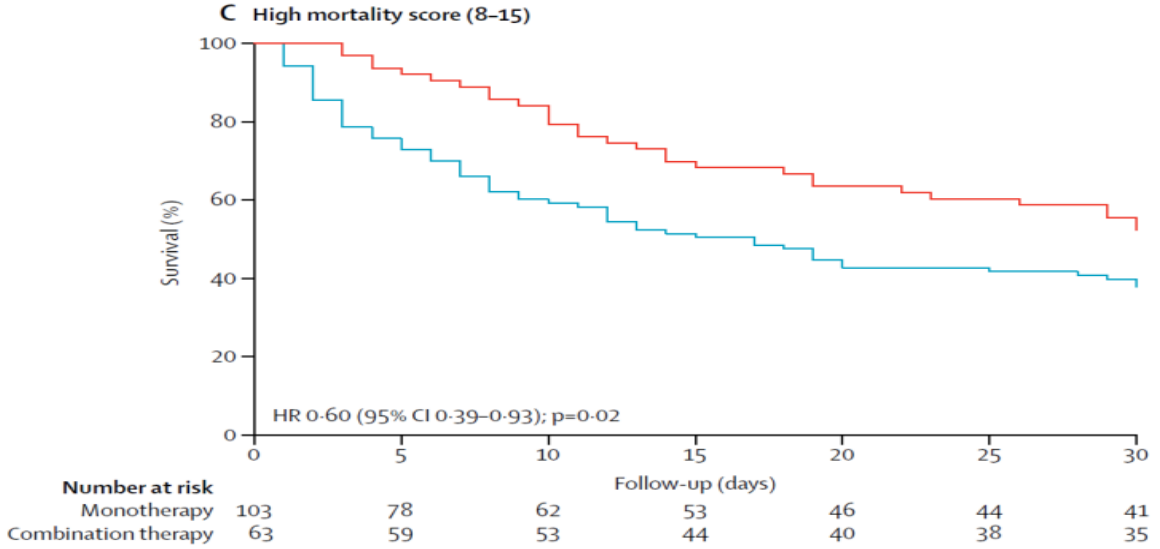
Tumbarello M et al JAC 2015; 70: 2133

Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study

Belén Gutiérrez-Gutiérrez, Elena Salamanca*, Marina de Cueto, Po-Ren Hsueh, Pierluigi Viale, José Ramón Paño-Pardo, Mario Venditti, Mario Tumbarello, George Daikos, Rafael Cantón, Yohei Doi, Felipe Francisco Tuon, Ilias Karaiskos, Elena Pérez-Nadales, Mitchell J Schwaber, Özlem Kurt Azap, Maria Souli, Emmanuel Roilides, Spyros Pournaras, Murat Akova, Federico Pérez, Joaquín Bermejo, Antonio Oliver, Manel Almela, Warren Lowman, Benito Almirante, Robert A Bonomo, Yehuda Carmeli, David L Paterson, Alvaro Pascual, Jesús Rodríguez-Baño, and the REIPI/ESGBIS/INCREMENT Investigators†*



aOR=1.21 (0.56-2.56) p=0.62



aHR=**0.56** (0.34-0.91) p=0.02

Lancet Infect Dis 2017

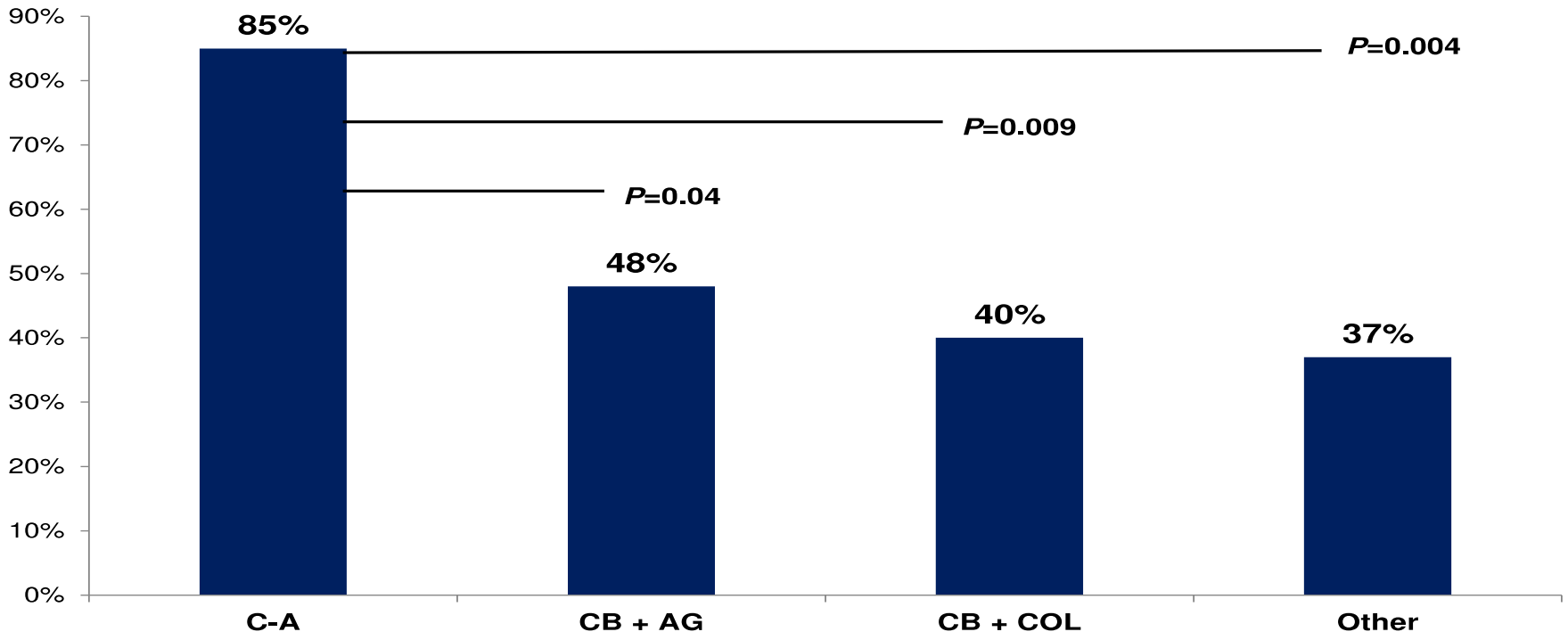
Multivariate Analysis of Factors Associated with all-cause 30-day Mortality of Patients with KPC BSIs

Variable	P	OR(95% CI)
Septic shock	0.008	7.17 (1.65-31.03)
APACHE	<0.001	1.04 (1.02-1.07)
Inadequate empirical Rx	0.003	4.17 (1.61-10.76)
Definitive Rx Col+tigecl+merop	0.01	0.11 (0.02-0.69)

Tumbarello M et al. CID 2012; 55: 943

Are the Newer Agents more Effective than the Old Ones

Ceftazidime-avibactam in the Treatment of Carbapenem-resistant *Klebsiella pneumoniae* BSIs



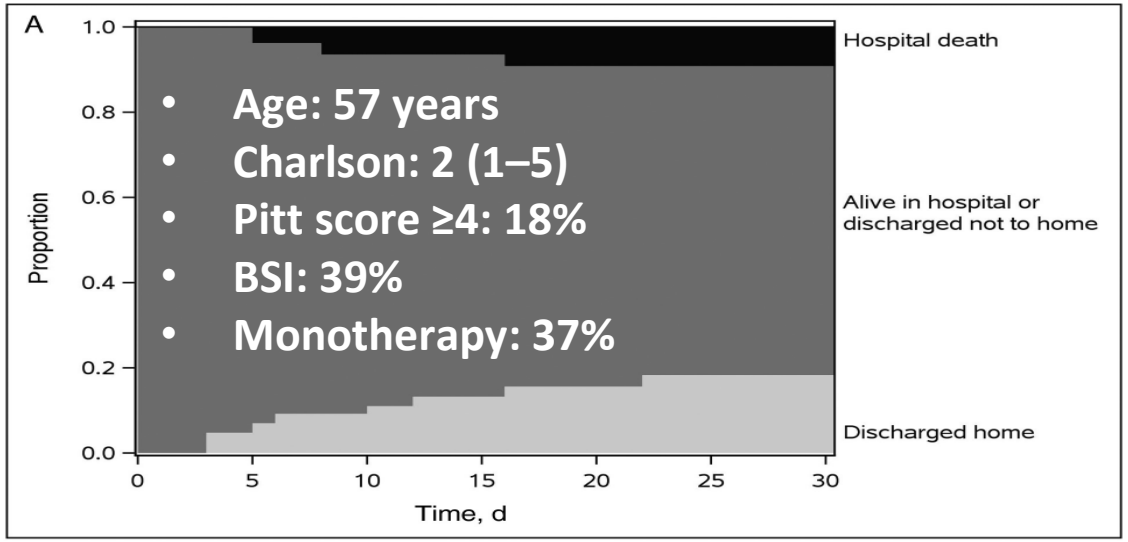
- 109 patients with BSIs, 50% ICU pts, median APACHE II 18
- 13 received C-A monotherapy (8) or combination (5)

- Primary bacteremia (OR=4.50, 95% CI: 1.53–13.21)
- Receipt of C-A (OR=8.64, 95% CI: 1.61–43.39) l

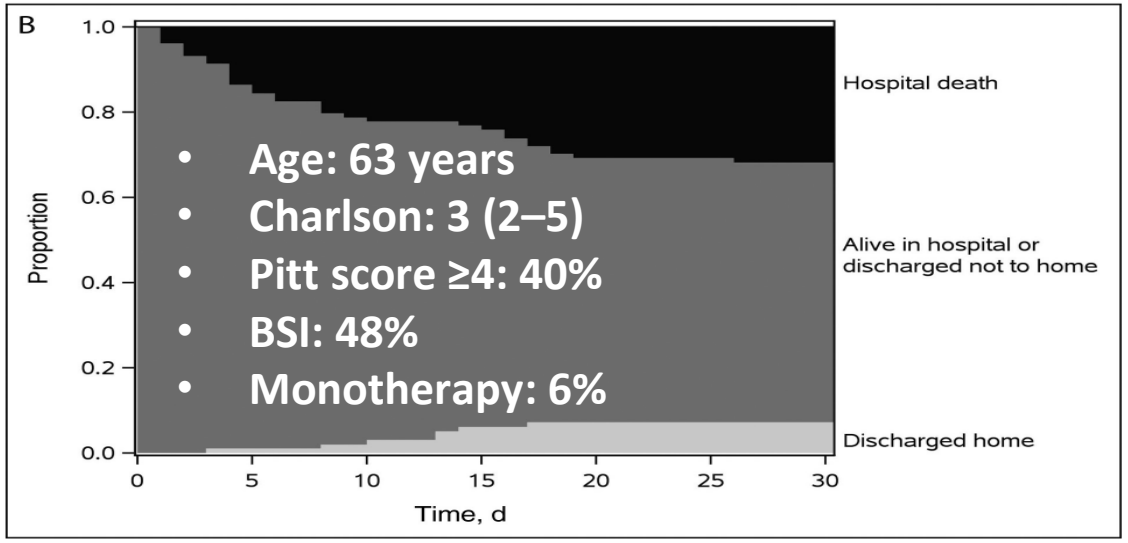
Shields RK et al. *Antimicrob Agents Chemother* 61:e00883-17.

Ceftazidime-avibactam vs. Colistin in the Treatment of Carbapenem-Resistant Enterobacteriaceae

CAZ-AVI (N=38)



Colistin (N=99



- IPTW-adjusted all-cause hospital mortality 30 days after starting treatment was 9% (C-A) versus 32% (CS)

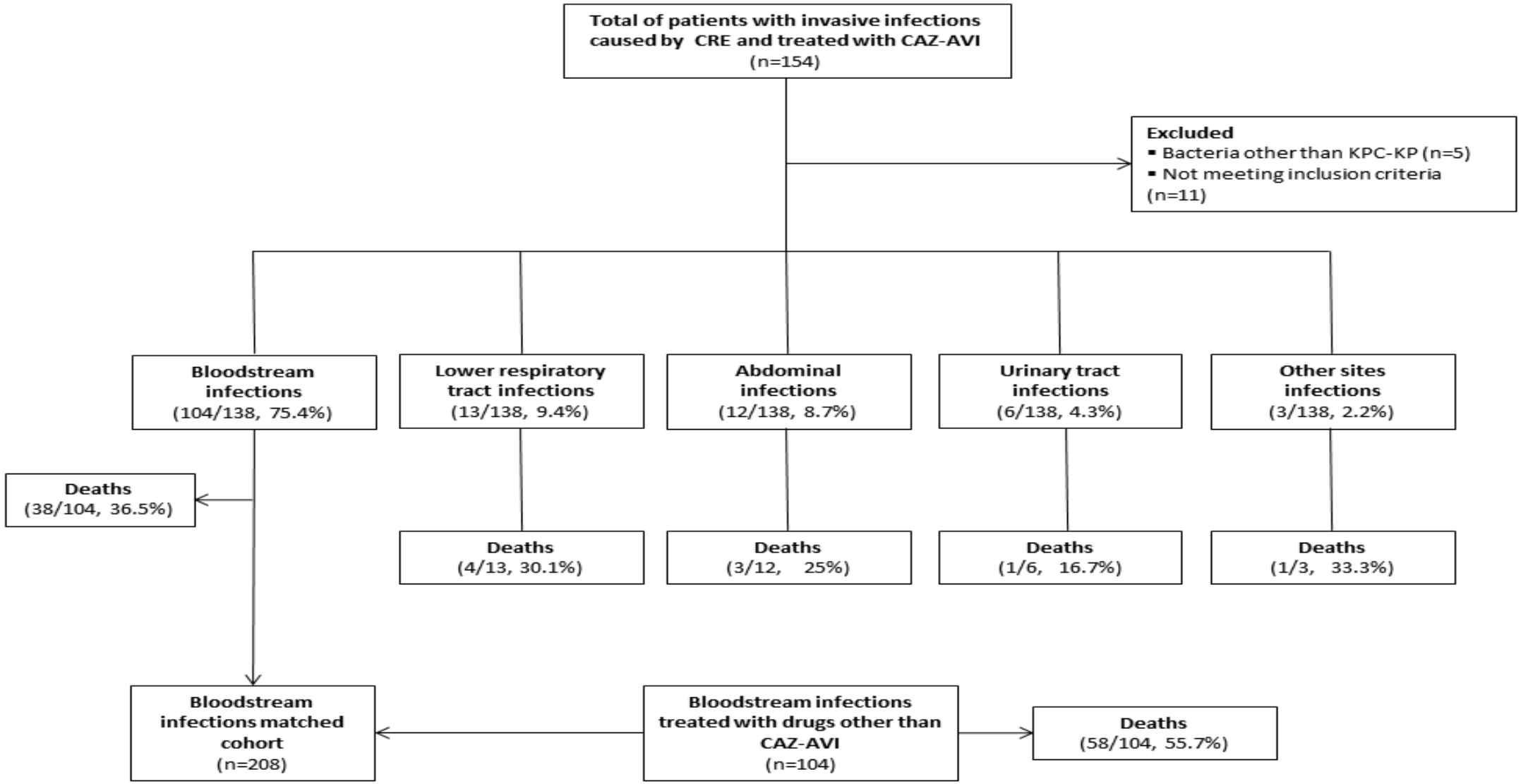
- Patients treated with ceftazidime-avibactam were less likely to die and more likely to be discharged home during the first 30 days after starting treatment

Van Duin V et al. *Clinical Infectious Diseases* 2018; 66: 163–71

CAZ-AVI for KPC-Kp Infections

Tumbarello M CID 2018 doi: 10.1093/cid/ciy492

No. of Patients	138
Age (median)	60
Charlson >3	47 (34.1%)
ICU	46 (33.3%)
Septic shock	43 (31.2%)
CAZ-AVI combination	109 (78.9%)
30-day mortality	47 (34.1%)
Relapse	12 (8.7%)
Resistance	3 (2.2%)



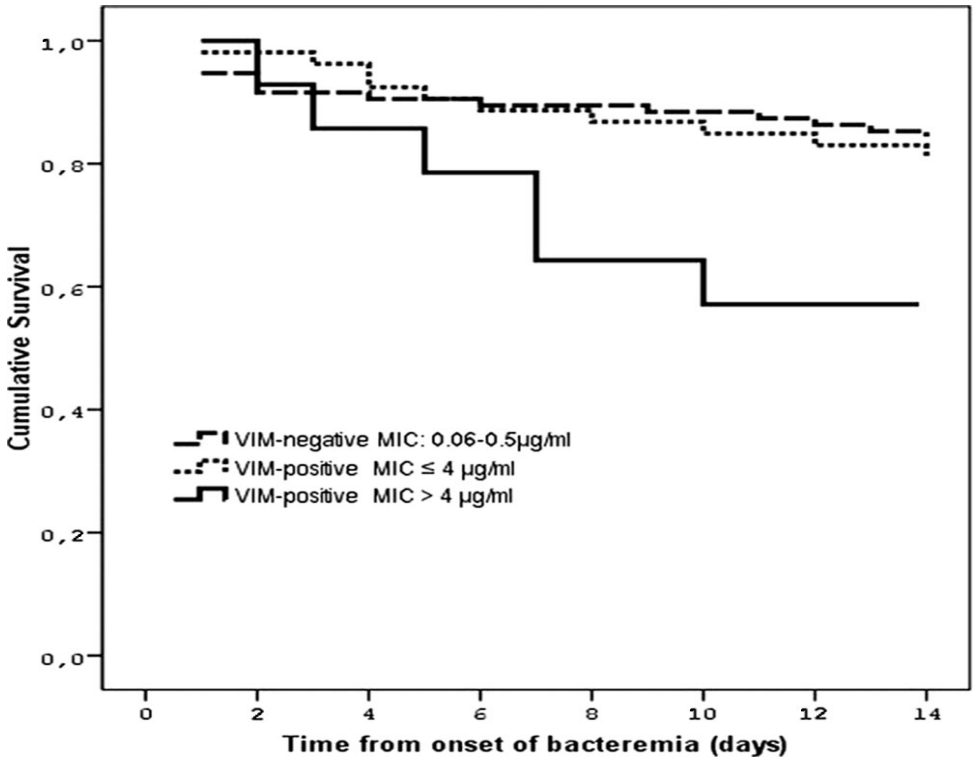
Tumbarello M CID 2018 doi: 10.1093/cid/ciy492

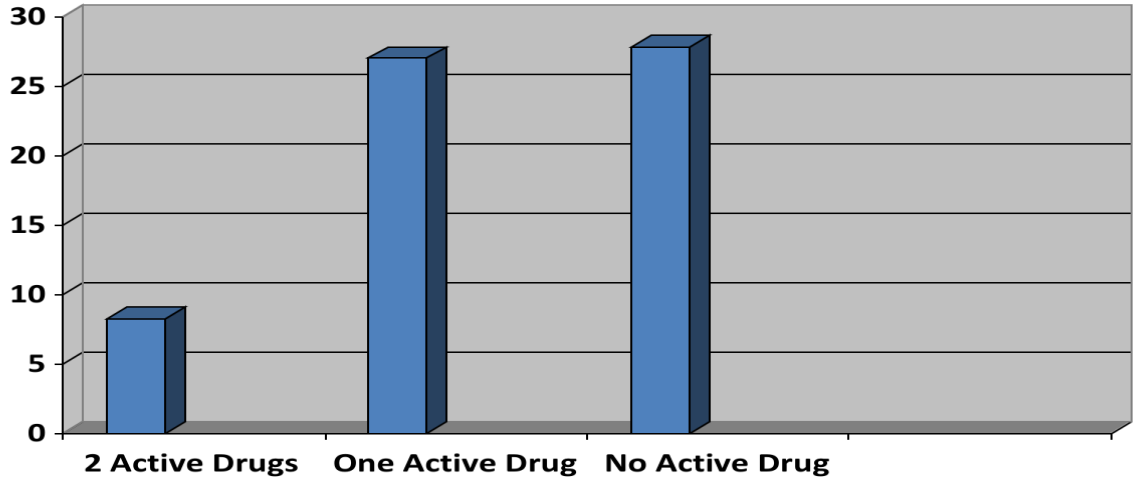
Factors Indepedendly Assosiated with Mortality in Patients with KPC-Kp BSIs

Variable	OR (95%CI)	*P*
Mechanical ventilation	4.31 (1.99-9.33)	<0.001
Charlson >3	3.3 (1.61-6.77)	0.001
Neutropenia	3.36 (1.25-8.75)	0.03
Septic Shock	2.94 (1.46-5.92)	0.003
CAZ-AVI treatment	0.27 (0.13-0.57)	0.001

Tumbarello M CID 2018 doi: 10.1093/cid/ciy492

Outcomes of patients with VIM-Kpn BSIs according to susceptibility of the infecting organism to carbapenems and treatment regimens





Daikos GL AAC 2009; 53:1868

Bacteraemia due to OXA-48-carbapenemase-producing Enterobacteriaceae: a major clinical challenge

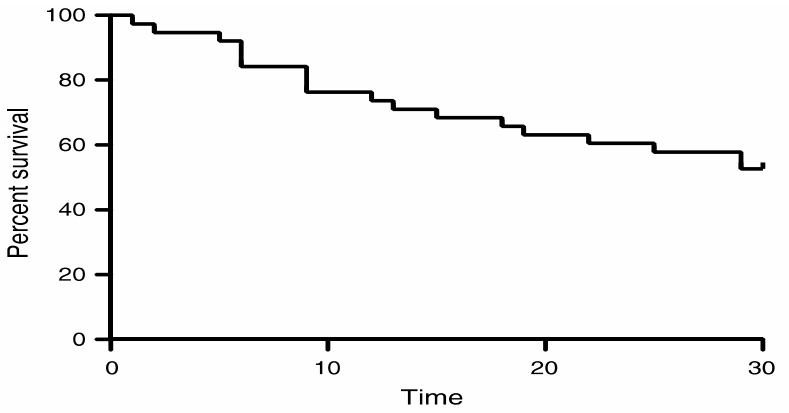
Clin Microbiol Infect 2012; 19: E72–E79

C. Navarro-San Francisco[1], M. Mora-Rillo[1], M. P. Romero-Gómez[2], F. Moreno-Ramos[3], A. Rico-Nieto[1], G. Ruiz-Carrascoso[2], R. Gómez-Gil[2], J. R. Arribas-López[1], J. Mingorance[2] and J. R. Paño-Pardo[1]

- 40 patients with BSIs
- 35 Kpn, 5 E. coli
- 23 pts with comorbididies
- 18 pts Severe sepsis/shock

Treatment	All patients (n = 34)	Patients alive at day 30 after onset of BSI (n = 19) (%)	Patients dead at day 30 after onset of BSI (n = 15) (%)
Monotherapy			
Colistin	1	1 (5.2)	0 (0)
Tigecycline	2	2 (10.5)	0 (0)
Amikacin	3	2 (10.5)	1 (6.6)
Carbapenem	1	0 (0)	1 (6.6)
Total monotherapy	7	5 (26.3)	2 (13.3)
Combined therapy			
Two or more active drugs (carbapenem not included)	21	10 (52.6)	11 (73.3)
Two or more active drugs (carbapenem included)	6	4 (21.1)	2 (13.3)
Total combined therapy	27	14 (73.7)	13 (86.6)

Kaplan–Meier 30-day survival curve.



CRE OXA-48 Infections Treated with CAZ-AVI Patients Characteristics and Outcomes

- 24 patients; 15 as initial definitive Rx and 9 as salvage Rx CAZ-AVI monotherapy=14, combination=10
- IAI=7, Urinary=6, Respiratory=5, Other=6
  - Bacteremia=8, Septic shock=4
  - K. pneumoniae=23, E. coli=1
- Clinical cure=62.5%, 30-day mortality=8.3%
- Recurrence =7 patients
- Emergence of resistance = 0

De la Calle C IJAA doi.org/10.1016/j.ijantimicag.2018.11.015

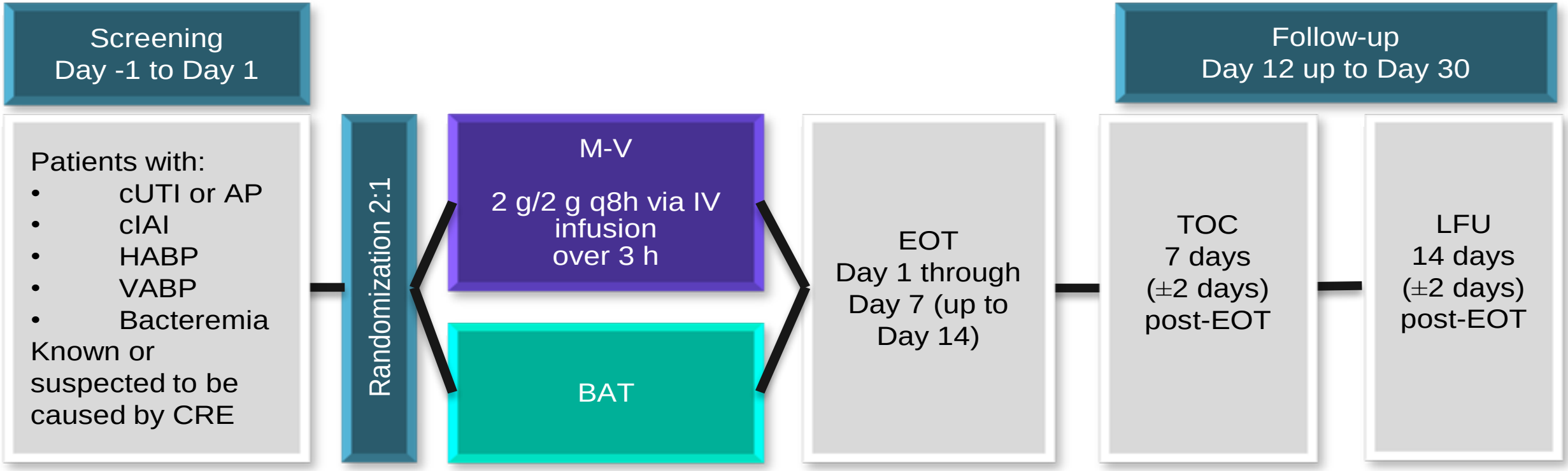
CRE-OXA-48 Infections Treated with CAZ-AVI
Patients Characteristics and Outcome

No. Ασθενών	57
Age (median)	64
Charlson (median)	3
ICU	22 (30%)
Bacteremia	26(46%)
Septic Shock	20 (35%)
INCREMENT CPE Score	6
CAZ-AVI monotherapy	46 (81%)
30-day mortality	12 (22%)
Relapse	6 (10%)
Resistance	0 (0%)

Sousa A JAC 2018 doi: 10.1093/jac/dky295

Meropenem-Vaborbactam vs BAT for CRE Infections

Figure 1. Study Schema

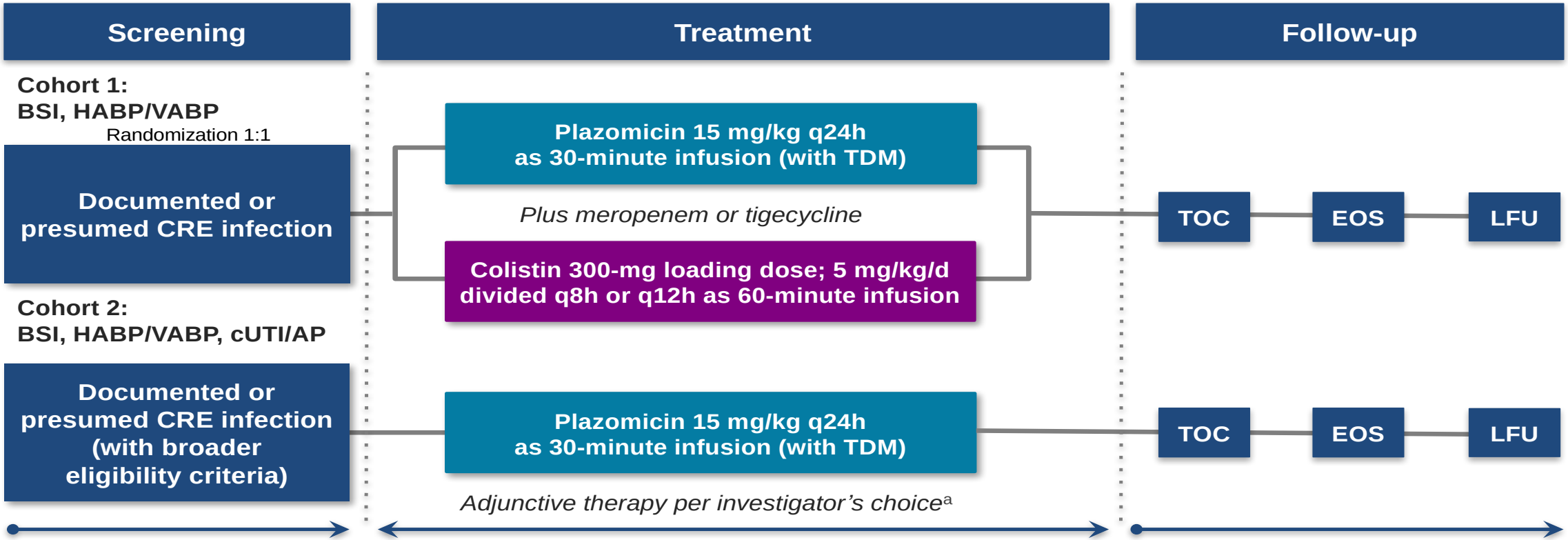


EOT, end of treatment; TOC, test of cure; LFU, last follow-up.

Wunderink R Infect Dis Ther 2018; 7: 439

(N=28) (N=15)

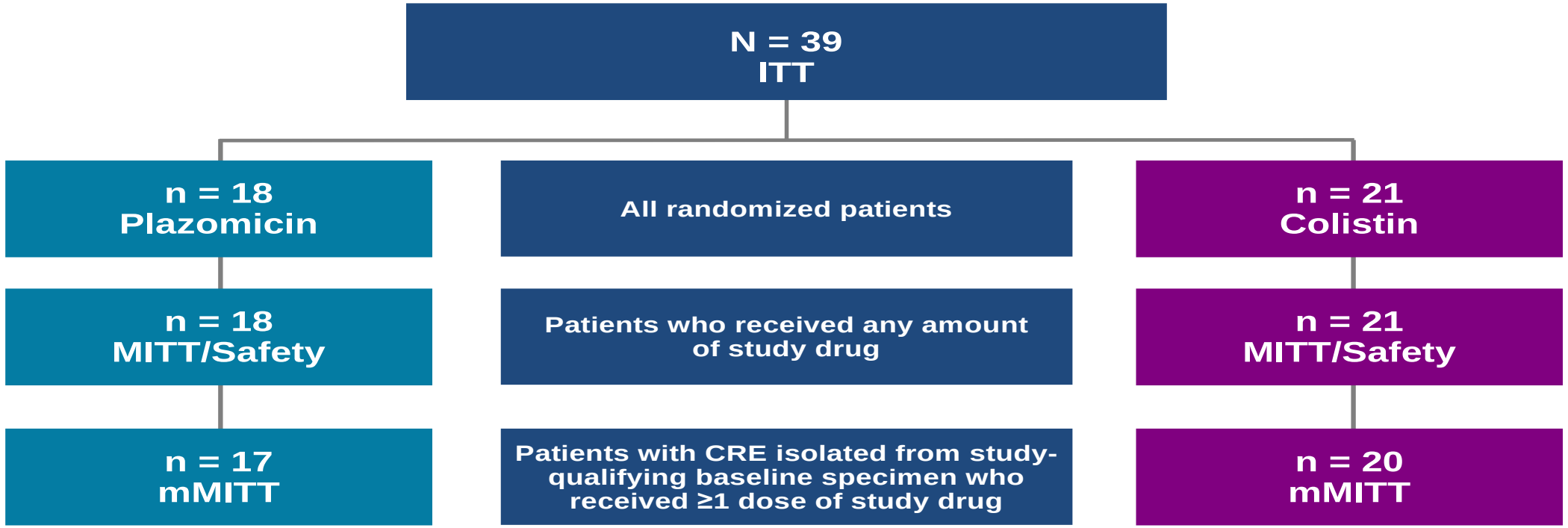
CARE Study Design



[a]Adjunctive therapy per investigator for BSI, HABP/VABP patients only; optional oral step-down after ≥4 days IV for cUTI/AP.
AP, acute pyelonephritis; cUTI, complicated urinary tract infection; EOS, end of study; LFU, late follow-up; q8h, every 8 hours; q12h, every 12 hours; q24h, every 24 hours; TDM, therapeutic drug management; TOC, test of cure.

DOI: 10.1056/NEJMc1807634

CARE Patient Disposition (Randomized Cohort 1)



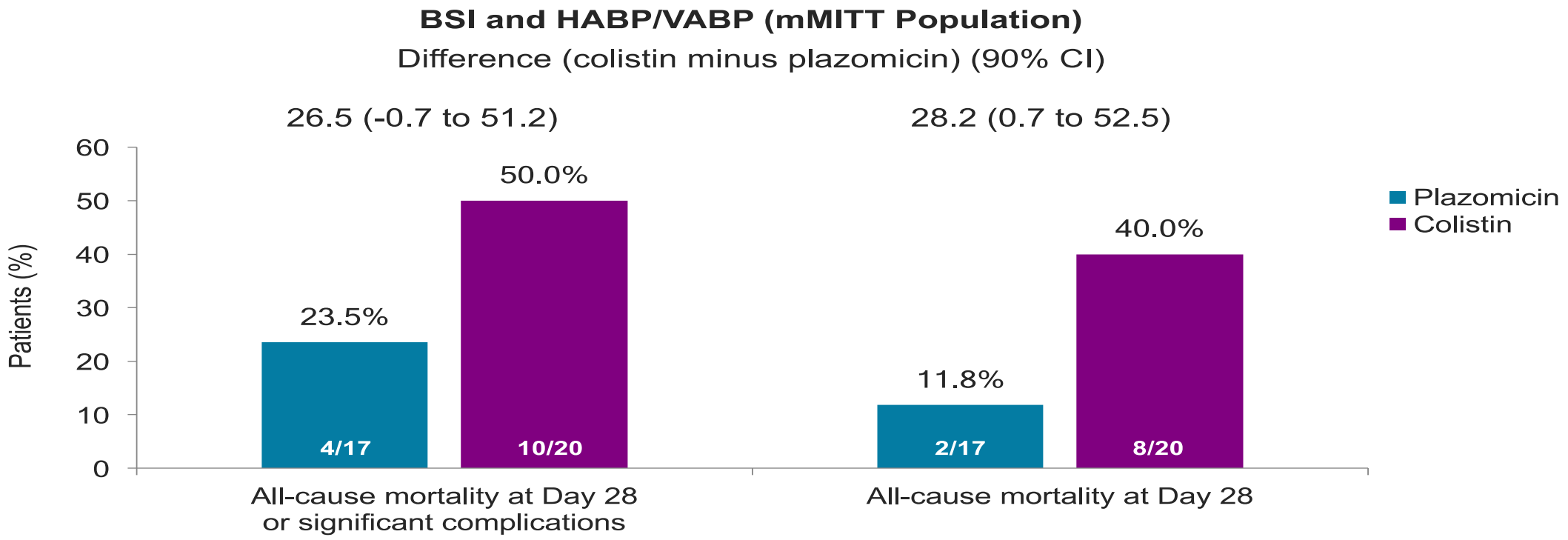
Primary efficacy analysis population included patients with BSI or HABP/VABP due to CRE.
CRE defined as meropenem MIC of ≥4 µg/mL, or a meropenem MIC of 2 µg/mL and disk diffusion zone ≤19 mm on central laboratory testing.

ITT, intent to treat; MIC, minimum inhibitory concentration; MITT, modified intent to treat; mMITT, microbiological modified intent to treat.

DOI: 10.1056/NEJMc1807634

CARE Efficacy Results (Randomized Cohort 1)

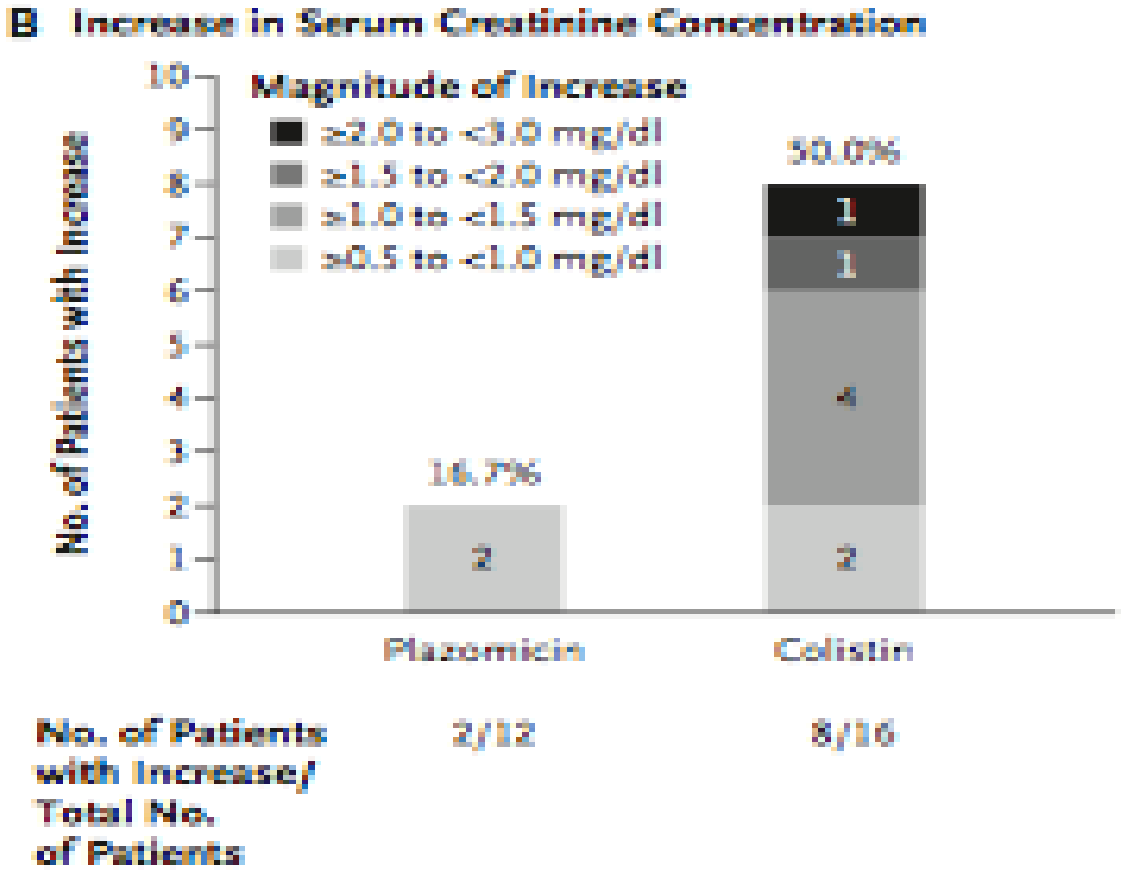
Reduced Mortality at Day 28 for Plazomicin Versus Colistin



Two-sided 90% confidence interval (CI) calculated based on the unconditional exact method.

DOI: 10.1056/NEJMc1807634

Number of patients with an increase in serum creatinine of 0.5 mg/dl or more



DOI: 10.1056/NEJMc1807634

Is There Effective Therapy Against MBL-producers?

Mechanism-based Strategy

- For MBLs (VIM, NDM, IMP)
  - Aztreonam plus anti-ESBL agent
- For NDM-OXA-48 or NDM-KPC
  - Aztreonam plus CAZ-AVI

Aztreonam plus clavulanate, tazobactam or avibactam for the treatment of metallo-β-lactamase-producing-Gram negative related infections

	MICs (mg/L)						
	ATM	CZA	C/T	AMC	ATM + CZA	ATM + C/T	ATM + AMC
A-10 + CMY-16 + TEM-1	32	>256	>256	16	0.125	24	8
+ TEM-1	>256	>256	>256	12	1	>256	2
+ OXA-2 + CTX-M-15 + TEM-1	>256	>256	>256	24	2	>256	8
M-15 + TEM-1	>256	>256	>256	32	6	>256	8
X-M-15 + OXA-1	>256	>256	>256	96	6	>256	4
CTX-M-15 + CMY-6	>256	>256	>256	>256	6	>256	24
+ TEM-1 + CTX-M-15	>256	>256	>256	96	8	>256	64

According to CLSI breakpoints, aztreonam susceptibility was fully restored for 86%, 20% and 50% of the MBL-producing Enterobacteriaceae when combined with ceftazidime-avibactam, ceftolozane-tazobactam and amoxicillin-clavulanate

AAC doi:10.1128/AAC.00010-19

J Antimicrob Chemother
doi:10.1093/jac/dkx496

Clinical outcomes after combination treatment with ceftazidime/avibactam and aztreonam for NDM-1/OXA-48/CTX-M-15-producing *Klebsiella pneumoniae* infection

Evelyn Shaw[1,2]*, Alexander Rombauts[1], Fe Tubau[3,4], Ariadna Padullés[5], Jordi Càmara[3], Toni Lozano[5], Sara Cobo-Sacristán[5], Núria Sabe[1,2], Imma Grau[1,4,6], Raül Rigo-Bonnin[7], M. Angeles Dominguez[2,3,6] and Jordi Carratalà[1,2,6]

- 10 pts were treated with Ceftazidime/avibactam plus aztreonam
- 5 had bloodstream infection
- Clinical success 6/10
- 3 deaths
- 1 recurrence

Optimizing Current Treatment Options

- **Carbapenems**
- High dose, prolonged infusion, or continuous infusion with TDM
- **Colistin**
- Loading dose, preferably in combination when the MIC of the infecting organism > 0.5mg/L
- **Fosfomycin**
- For systemic infections 6 g IV q 6 h, always in combination with another active agent
- **Tigecycline**

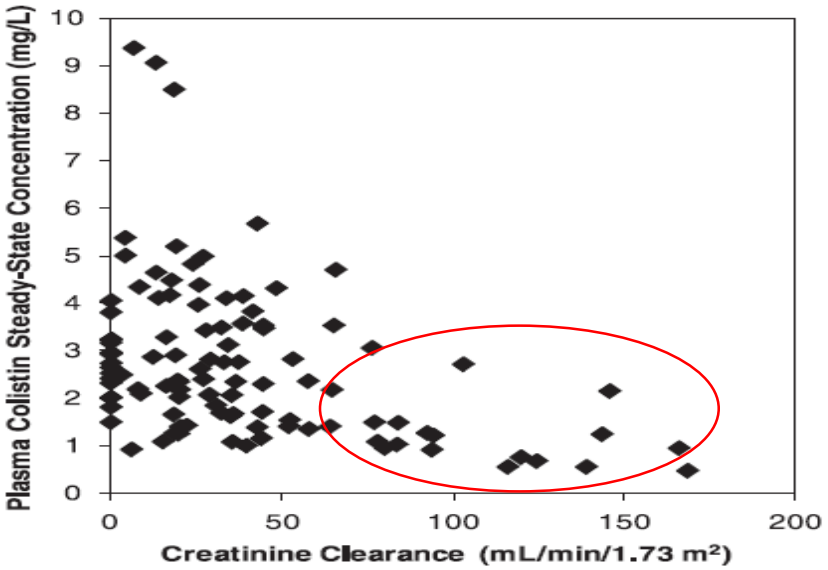
- Optimize PK/PD with high dose (100mg q 12h)

- **Aminoglycosides**

- Once daily, high dose (Gentamicin 7mg/kg) with TDM

Patients with Increased CrCL

Garonzik et al, AAC 2011 & ECCMID 2013
Karaiskos et al, AAC 2015; 59: 7240



In patients with high CrCL there is decreased ability to reliably attain plasma colistin Css,avg ≥ 2mg/L

Only 11/39 patients with CrCl > 80 attained Css,avg ≥ 2mg/L (1)

Only 4/12 patients with CrCl > 80 attained Css,avg ≥ 2mg/L (2)

Creatinine Clearance (ml/min/1.73m²)	Proportion of pts who attained a plasma colistin - Css,avg ≥2 mg/L	
	Garonzik et al	Karaiskos et al
80 – 99	3/7	2/5
100 – 119	6/16	0/2
120 – 139	1/10	1/2
>140	1/6	1/3

Suboptimal treatment with colistin monotherapy

- MIC of the infecting organism > 0.5mg/L
- Pneumonia
- Clcr > 80ml/min

Table 3. 'Look-up' table of daily doses of colistimethate for a desired target plasma colistin $C_{ss,avg}$ of 2 mg/L for narrow windows of creatinine clearance

Creatinine clearance (mL/min)	Dose of colistimethate for plasma colistin $C_{ss,avg}$ of 2 mg/L[a]	
	mg CBA per day	Million IU per day
0	130	3.95
5 to <10	145	4.40
10 to <20	160	4.85
20 to <30	175	5.30
30 to <40	195	5.90
40 to <50	220	6.65
50 to <60	245	7.40
60 to <70	275	8.35
70 to <80	300	9.00
80 to <90	340	10.3
≥90	360	10.9

daily dose for a plasma colistin $C_{ss,avg}$

The suggested dose is 440 mg CBA per day (~13 million IU per day).

Nation R CID 2016

International Consensus Guidelin

Pharmacotherapy 2019;39:10–39 doi: 10.1002/phar.2209

Clinical Microbiology and Infection 24 (2018) 133–144

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journal homepage: www.clinicalmicrobiologyandinfection.com

Review

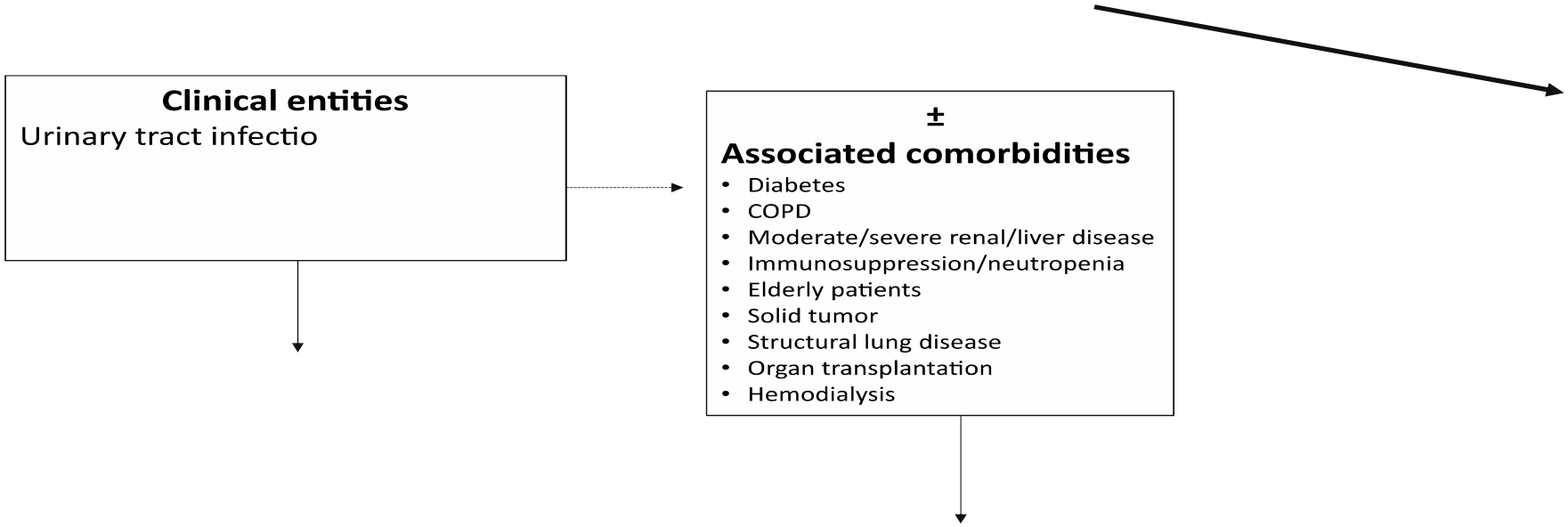
Management of KPC-producing *Klebsiella pneumoniae* infections

M. Bassetti [1, *], D.R. Giacobbe [2], H. Giamarellou [3], C. Viscoli [2], G.L. Daikos [4], G. Dimopoulos [5], F.G. De Rosa [7], E.J. Giamarellos-Bourboulis [6], G.M. Rossolini [8, 9], E. Righi [1], I. Karaiskos [3], M. Tumbarello [10], D.P. Nicolau [11, 12], P.L. Viale [13], G. Poulakou [1], on behalf of the Critically Ill Patients Study Group of the European Society of Clinical Microbiology and Infectious Disease (ESCMID), Hellenic Society of Chemotherapy (HSC) and Società Italiana di Terapia Antinfettiva (SITA)[†]

Revi

Criteria Leading to the Selection of Newer Agents

Montravers P DOI:10.1097/QCO.0000000000000490



Clinical Prediction Tools

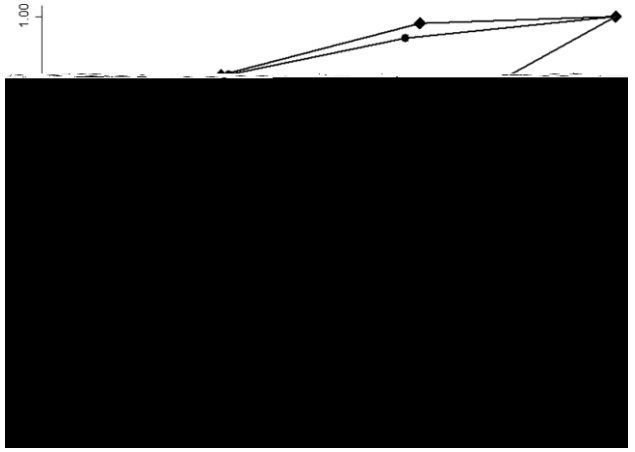
- Local Epidemiology
- Individual patient risk factors
  - Co-morbid conditions
  - Cumulative exposure to antibiotics
  - Prior hospitalization
  - Surgery or other interventions
- Infection-related factors
  - ICU, non-ICU
  - Source of infection
  - Severity of infection

Prediction Score for KPC-Kp Colonization or Infection

Variable	Points
Charlson ≥3	1
Neutropenia	1
Recent surgery <1 month	1
Two recent hospitalizations <12 months	1
Recent use of carbapenems or quinolones <3 months	1+1
CVC <1 month	1

- Score ≥ 3
- Predictive power
  - OR: 10.25 (95% CI: 7.57-13.91)
  - Area under receiver operating curve 0.82

Tumbarello et al AAC 2014; 58: 3514



Case 1

- 30 year old male with AML after induction chemotherapy presented with fever 39^0C, RR:24/min, HR: 100/min, BP: 110/60
- Two sets of blood cultures were drawn and the patient was started on Pip/tazo
- The 4^{th} day of treatment on Pip/tazo he became afebrile
- Blood cultures grew *E. coli*, susceptible to BLBLI, 2^{nd} and 3d generation cephalosporines, carbapenems and aminoglycosides
- The 10^{th} day of treatment, while he was on Pip/tazo, he had new onset of fever $38,5^0$C and persistent neutropenia (<100 PMNs/µl). RR:30/min, HR: 110/min, BP: 90/60

Case 1 (cont/d)

- Two sets of blood cultures were drawn and his treatment was changed to meropenem
- During his hospitalization he was found to be carrier of KPC-Kp (perirectal swab cultures positive)
- Is the above treatment adequate for this particular patient?

From Colonization to Infection

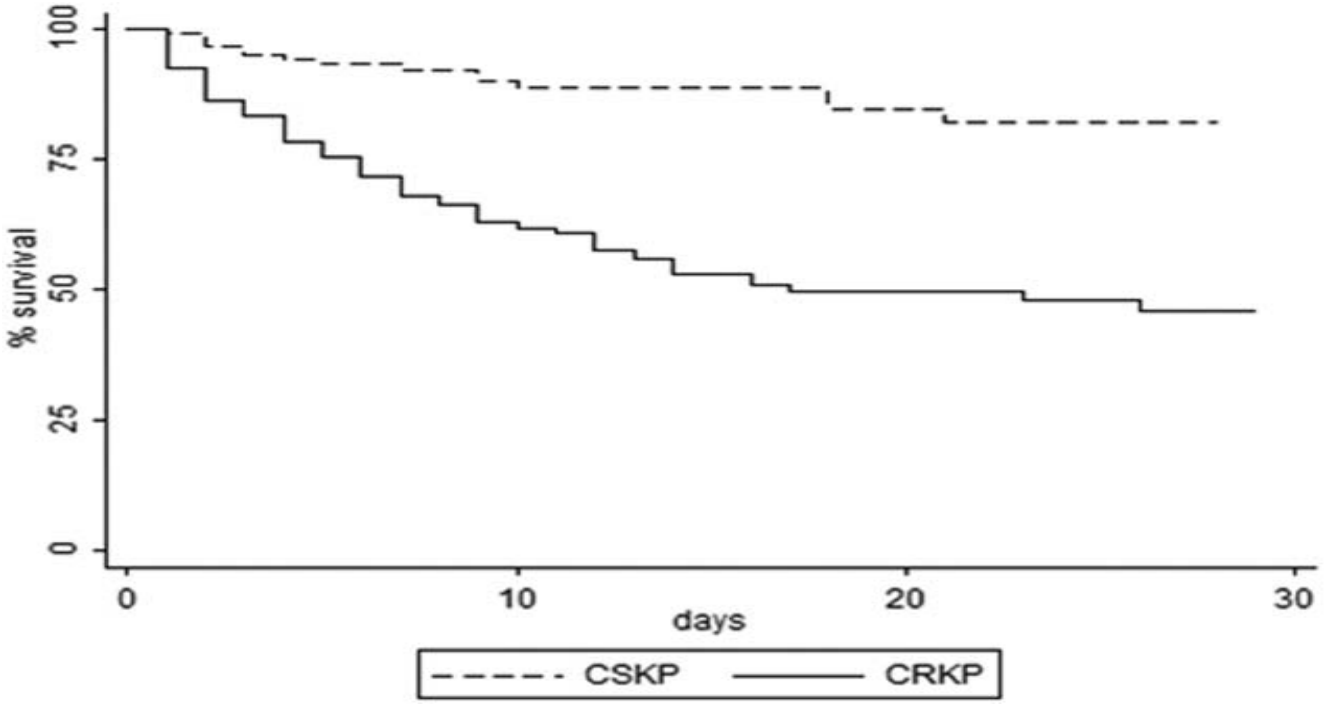
Host	%
Normal host	10
Neutropenic	25
Autologous HSCT	26
Allogeneic HSCT	40

C Girmenia Bone Marrow Transplantation 2014 doi:10.1038/bmt.2014.231

- 50 to 60% of hematology patients with infections caused by ESBL-producers receive inappropriate initial therapy (Gudio JAC 2010, Ortega JAC 2009, Tumbarello AAC 2006)

- Among 50 hematology pts, hospitalized in 3 tertiary care hospitals in Greece, with BSIs caused by CP-Kp 17 (34%) received inappropriate empirical therapy (Tofas P IJAA 2016)

Mortality in patients with Hematologic Malignancies and BSI Caused by CR-Kp και CS-Kp



Trecarichi EM Am J Hematol 2016;91:1076

ECIL Guidelines for Empirical Treatment of Febrile Neutropenia

De-escalation strategy

- De-escalation should be applied for patients
  - With complicated presentations
  - With individual risk factors for resistant pathogens
  - In centers where resistant pathogens are regularly seen at the onset of febrile neutropenia

Klebsiella pneumoniae

Ampicillin/sulbactam	R
Pip/tazo	R
Cefoxitin	R
Cefepime	R
Ceftazidime	R
Gentamicin	2 mg/L
Meropenem	MIC=>8mg/L
Aztreonam	R
Ceftazidime/avibactam	1/4 mg/L
Colistin	MIC=1 mg/L
Tigecycline	MIC=2 mg/L
Fosfomycin	MIC=32 mg/L

Case 1 cont/d

- Older or newer agent?
- Ceftazidime/avibactam or meropenem/vaborbactam
- Monotherapy or combination?

Case 1 cont/d

- The patient was started on Ceftazidime/avibactam 2.5g IV q 8hrs plus gentamicin 5mg/kg

- Gentamicin was discontinued after 5 days

CAZ-AVI vs Meropenem/Vaborbactam

- Retrospective observational study
- Study period: 2015-2018
- CRE infections except UTIs, 40% BSIs
- Rx with either agent ≥ 72hrs

- Primary outcome, clinical success
  - 30-day survival
  - Resolution of signs and symptoms
  - Clearance of bacteremia at day-7
  - No recurrence within 90 days

Ackley R IDWeek 2019; abstract No. 662

CAZ-AVI vs Meropenem/Vaborbactam

Outcome	CAZ-AVI N=105	Meropenem-Vaborbactam N=26	P
Monotherapy/combination	41/64	19/3	<0.01
Clinical success	65/105	15/22	0.49
Recurrence	15/105	3/22	0.2
MIC increase	6/105	0/22	0.13
Resistance	3/105	0/22	0.21

Ackley R IDWeek 2019; abstract No. 662

Case 2

- 70 years old male s/p left hemi-colectomy and anastomosis due to colon Ca. The 7th post/operative day he developed fever up to 39.5°
- BP: 90/80, HR: 120/λεπτό, T=38.5° C
- WBC=25K/μl, PLT 50K/μl, Creatinine 2.5mg/dl.
- Chest CT atelectasis in lower lobe of R lung
- CT of abdomen: Free air and loculated fluid collection in peritoneal cavity close to anastomosis.
- The patient underwent second operation to close leaking of anastomosis
- He was started on meropenem and transferred to ICU

Case 2 cont/d

- Cultures of peritoneal fluid grew ESBL-producing E coli and he continued treatment with meropenem
- The patient continued to have fever an he was operated for third time to restore the leaking at anastomosis site

- Peritoneal fluid cultures grew Pseudomonas aeruginosa

Ps aeruginosa

Ampicillin/sulbactam	R
Pip/tazo	R
Ceftazidime	R
Cefepime	R
Amikacin	R
Gentamicin	R
Meropenem	R
Aztreonam	R
Ceftolozane/tazobactam	1/4 mg/L
Colistin	MIC=1 mg/L
Fosfomycin	R

What Makes Ceftolozane/Tazobactam Different? Activity vs. *Pseudomonas aeruginosa*

- Stable against common *P. aeruginosa* resistance mechanisms, including loss of outer membrane porin (OprD), chromosomal AmpC, and up-regulation of efflux pumps (MexXY, MexAB)[1]
- Isolates resistant to other cephalosporins may be susceptible, although cross-resistance may occur[2]

Resistance Mechanisms	Outer Membrane Porin Loss OprD	β-lactamase Enzyme AmpC	Efflux Pump MexXY	Efflux Pump MexAB
Ceftolozane				
Ceftazidime				
Cefepime				
Piperacillin/tazobactam				
Imipenem				
Meropenem				

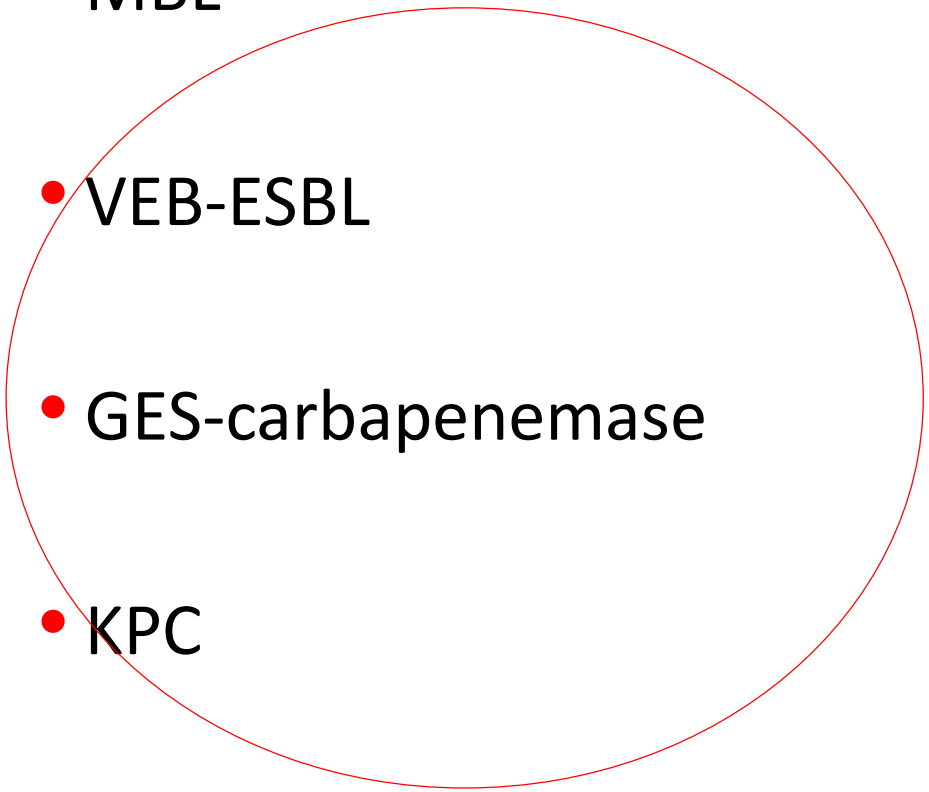
Activity greatly decreased >> Retains activity

Table adapted from Castanheira M, *et al.* 2014

1. Castanheira M, *et al. Antimicrob Agents Chemother.* 2014;58:6844-6850.
2. ZERBAXA [prescribing$_2$ information]. Cubist Pharmaceuticals; Lexington, MA; 2014.

Pseudomonas aeruginosa Mechanisms of Resistance

- Efflux
- Derepressed AmpC
- OprD
- MBL
- VEB-ESBL
- GES-carbapenemase
- KPC

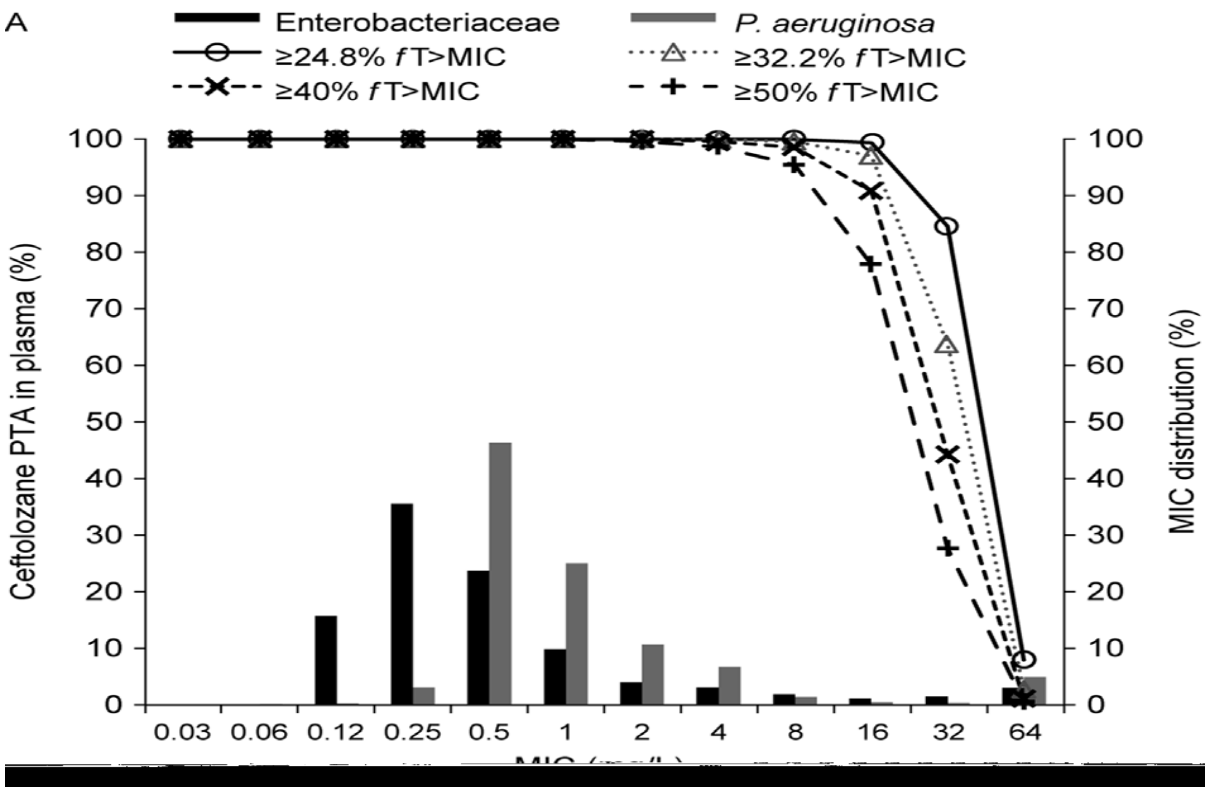


Livermore D doi:10.1093/jac/dkx136
Livermore D doi:10.1093/jac/dkx438

ACCP
American College of Clinical Pharmacology
Advancing Clinical Care through Pharmacology®

Ceftolozane/Tazobactam Pharmacokinetic/ Pharmacodynamic-Derived Dose Justification for Phase 3 Studies in Patients With Nosocomial Pneumonia

The Journal of Clinical Pharmacology
2016, 56(1) 56–66
© 2015 The Authors. *The Journal of Clinical Pharmacology* published by Wiley Periodicals, Inc. on behalf of American College of Clinical Pharmacology
DOI: 10.1002/jcph.566



C/T 3g q 8h
50% *f*T>MIC
PTA for ELF 88% for
Isolates with MIC 8mg/L

Risk for MDR Organisms

Patients :

- Prior administration of broad spectrum antibiotics

-

- **Underlying comorbidities** (neutropenia, severe immunosuppression, structural lung disease, solid tumour)
- **Previous colonization by MDR/XDR *P. aeruginosa* strain?**
- **Previous therapy (within 3 months) with an antipseudomonal -lactam?**
- **Hospital setting with a prevalence >15-20% of MDR *P. aeruginosa***

YES

(at any)

NO (to all)

BACKBONE DRUG

Ceftolozane- tazobactam > ceftazidime-avibactam> meropenem> piperacillin-tazovactam/ ceftazidime/ cefepime

PLUS

SECOND ANTI-PSEUDOMONAL AGENT

Aminoglycoside/ colistin/ fosfomycin> fluoroquinolones

ALWAYS CONSIDER AN ADEQUATE SOURCE CONTROL OF INFECTION

BACKBONE DRUG

Piperacillin/tazobactam/ carbapenem (maily meropenem)/ ceftazidime/ cefepime

Case 3

- A 68 yo male with history of prostate Ca was admitted to ICU because of new onset of dyspnea, chest pain and hemoptysis. On his arrival he was intubated. CT pulmonary angiography revealed multiple pulmonary emboli and he was started on fondaparinux.
- On 7th day, he was hemodynamically stable on ventilation with FIO_2 40%. Routine screening for colonization revealed KPC-Kp in rectal swabs and bronchial secretions and ABC in bronchial secretions.
- On 10th day, while on ventilator, he developed fever, increased purulent bronchial secretion, new infiltrates on CXR.
- Blood, urine and bronchial aspirates were sent for cultures and he was started on meropenem and colistin.

Critical Care

RESEARCH Open Access

Multidrug resistance, inappropriate empiric therapy, and hospital mortality in *Acinetobacter baumannii* pneumonia and sepsis

Marya D. Zilberberg[1*], Brian H. Nathanson[2], Kate Sulham[3], Weihong Fan[3] and Andrew F. Shorr[4]

- Patients with MDR-AB were more likely to receive IET than those in the non-MDR-AB group (76.2 % vs. 13.8 %, $p < 0.001$).
- MDR-AB strongly predicted receipt of IET (adjusted RRR 5.5, 95 % CI 4.0–7.7, $p < 0.001$).
- IET exposure was associated with higher hospital mortality (adjusted RRR 1.8, 95 % CI 1.4–2.3, $p < 0.001$).

Ri f. :tors fo arbapenem-resistant *Klebsiella pneumoniae* bloodstream n :ti on amon rectal carriers: a prospective observational multicentre t ly

Clin Mi robiol Infect **2014**; 20:1357–62

I. ianne E. M. Tre :, F. G. De Rosa[3], V no[4], M. Bassetti[5], R. E. Lewis[1], A. R. Losito[2], S. Corcione[3], C. Saffioti[4],
1. artol G. Mai , C S. Cardellino[3], S. auda[2], C. Viscoli[4], P. Viale[1] and M. Tumbarello[2]

TABLE 2. L ci e, sion ana vsis of risk factors for CR-KP BSI deve men n rect iers

	OR (95% CI)	P-va	Risk score
Admission to ICU	1.65 (1.05–2.59)	0.03	2
Invasive abdominal procedures	1.87 (1.16–3.04)	0.01	3
Chemotherapy/radiation therapy	3.07 (	<0.0001	4
Colonization at site besides stool (risk per each additional site)			site

ICU, intensive car

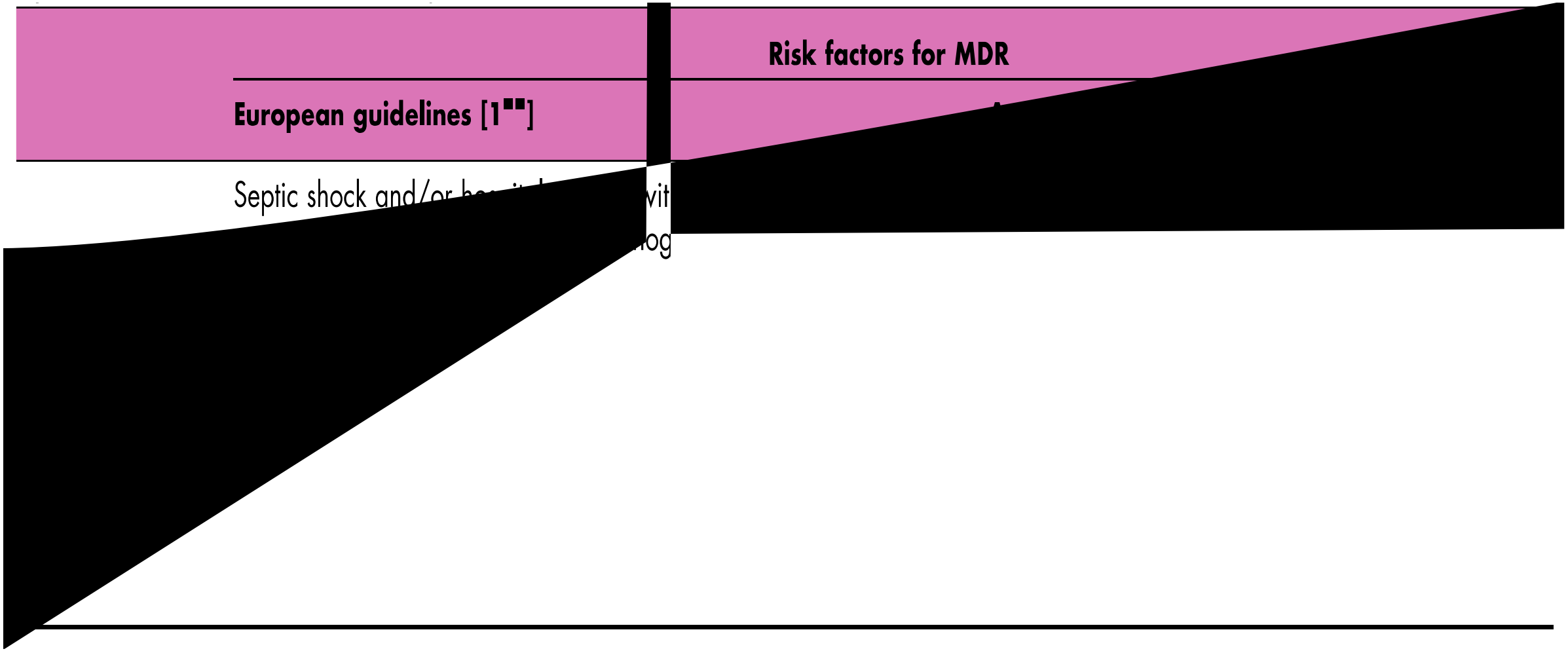
V ation of the scor

- Sc l

85%

Risk Factors for MDR HAP/VAP

Bassetti et al Curr Opin Crit Care 2018, 24:385 – 393



Case 3 Cont/d

- The patient was started on Ceftazidime/avibactam 2.5 g q 8hrs and colistin 9MU loading dose followed by 4.5MU q 12hrs

- Bronchial aspirate grew *A baumannii* >10^6 CFU/ml

Antimicrobial Agents Used in the Treatment of CRAB Infections

Main agents

- Polymyxins
- Tigecycline
- Sulbactam

Newer agents

- Cefiderocol
- Erevacycline

Other agents

- Minocycline
- TMP/SMX
- Rifampin
- Fosfomycin
- Aminoglycosides

Acinetobacter baumannii

Ampicillin/sulbactam	R
Ampicillin/sulbactam	R
Cefoxitin	R
Cefepime	R
Ceftazidime	R
Gentamicin	R
Meropenem	R
Aztreonam	R
Ceftazidime/avibactam	R
Colistin	MIC=1 mg/L
Tigecycline	MIC=2 mg/L
Fosfomycin	R

Case 3 Cont/d

- What is the best available treatment for this patient?
- Combination or monotherapy

Colistin Monotherapy vs Combinations

- 250 patients with CRAB bacteraemia
- Colistin-containing combinations (n=214) vs colistin monotherapy (n=36)
- Colistin combinations resulted in
  - lower in-hospital mortality (52.2 versus 72.2%)
  - higher microbiologic eradication (79.9 versus 55.6%)

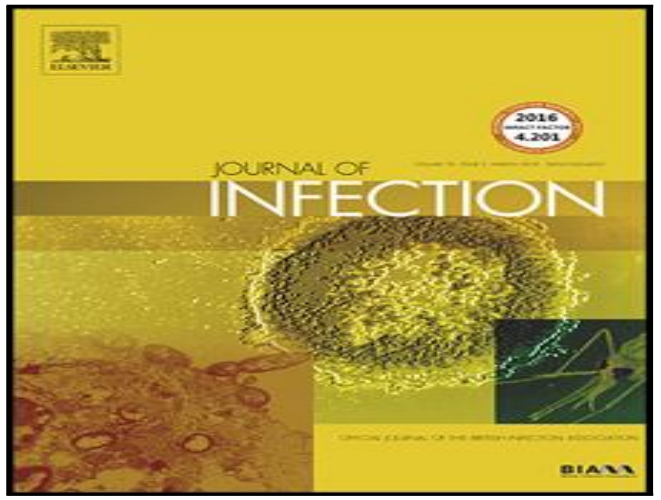
Batirel A Eur J Clin Microbiol Infect Dis. 2014;33:1311-22

Accepted Manuscript

doi.org/10.1016/j.jinf.2019.05.017

Bloodstream infections caused by carbapenem-resistant Acinetobacter baumannii: clinical features, therapy and outcome from a multicenter study

Alessandro Russo , Matteo Bassetti , Giancarlo Ceccarelli , Novella Carannante , Angela Raffaella Losito , Michele Bartoletti , Silvia Corcione , Guido Granata , Antonella Santoro , Daniele Roberto Giacobbe , Maddalena Peghin , Antonio Vena , Francesco Amadori , Francesco Vladimiro Segala , Maddalena Giannella , Giovanni Di Caprio , Francesco Menichetti , Valerio Del Bono , Cristina Mussini , Nicola Petrosillo ,



Variable	Hazard Ratio	95% CI	P
Septic shock	10.8	1.12-141	0.04
Charlson >3	1.44	1.04-2	0.02
Source control	0.22	0.01-0.42	0.01
Combination Rx	0.36	0.01-0.89	0.03

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Comparative efficacy and safety of treatment options for MDR and XDR *Acinetobacter baumannii* infections: a systematic review and network meta-analysis

- Network meta- analysis of 29 studies (four RCTs and 25 cohort studies). The investigators compared nine therapeutic options in terms of mortality, clinical cure and microbiologic eradication.
- No differences were observed in all-cause mortality among the different treatment regimens
- Colistin-based combinations were associated with significantly higher microbiologic eradication rates compared to colistin monotherapy, tigecycline monotherapy, or tigecycline in combination with other agents.

Randomized Controlled Trials (I)

- Colistin vs Colistin + Rifampicin (Durante-Mangoni et al)
  - 210 ICU pts with serious infections caused by XDR A. baumannii
  - **Colistin 2 MU x 3 (No loading dose) ± Rifampicin 600 mg x 2**
  - No significant diference in all-cause 30-day mortality (43,3% vs 42,9%)
  - Significant difference in microbiologic eradication (60.6% vs 44.8%, p=0.034)
- Colistin vs Colistin + Rifampicin (Aydemir et al)
  - 43 pts with VAP caused by XDR A. baumannii
  - **Colistin 4,5 MU/d (No loadinf dose) ± Rifampicin 600 mg/d**
  - No significant difference in terms of clinical response.
  - Faster micobiologic eradication with combination (4,5d vs 3,1d - p=0.029).

Clin Infect Dis 2013;57:349-58, *Epidemiol Infect*. 2013;141:1214-22

Randomized Controlled Trials (II)

- Colistin vs Colistin + Fosfomycin (Sirijatuphat et al)
  - 94 pts with CRAB infections
  - **Colistin 5mg CBA/Kg/d (No loading dose) ± Fosfomycin (iv) 4 g x 2**
  - No significant difference in all-cause 30 day mortality (53.8% vs 44.2%) or infection-related mortality (23.1% vs 16.3%)
  - Significant difference in microbiologic eradication in 72h (65.7% vs 87.8%, p=0.028)
- Colistin vs Colistin + Ampicillin/Sulbactam (Makris et al)
  - 39 pts with VAP caused by CRAB
  - **Colistin 3 MU x 3 (No loading dose) ± Ampicillin/Sulbactam 6 gr x 4**
  - No significant difference in all-cause 30 day mortality (63.2% vs 50.0%)
  - Significant difference in early clinical response (15.85% vs 70.0%, OR=12.4 p=0.001)

Antimicrob Agents Chemother. 2014;58:5598-601, *Indian J Crit Care Med*. 2018;22:67–77

Randomized Controlled Trials (III)

- Colistin vs Colistin + Meropenem (Paul et al, AIDA study)
  - 406 pts with serious infections caused by CR gram(-) organisms *A baumannii:* 312/406 (77%)
  - VAP/HAP: 45%, BSIs: 43%
  - **Colistin 4.5 MU x 2 (Loading dose) ± Meropenem 2 gr x 3 (Open-label)**
- **Composite outcome**
  - The patient alive at day 14
  - Haemodynamic stability (systolic blood pressure >90 mm Hg without need for vasopressor support),
  - Improved or stable SOFA score
  - Stable or improved oxygenation for patients with pneumonia
  - Microbiological cure for patients with bacteraemia

Lancet Infect Dis 2018;18:391-400

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial

Mical Paul, George L Daikos, Emanuele Durante-Mangoni, Dafna Yahav, Yehuda Carmeli, Yael Dishon Benattar, Anna Skiada, Roberto Andini, Noa Eliakim-Raz, Amir Nutman, Oren Zusman, Anastasia Antoniadou, Pia Clara Pafundi, Amos Adler, Yaakov Dickstein, Ioannis Pavleas, Rosa Zampino, Vered Daitch, Roni Bitterman, Hiba Zayyad, Fidi Koppel, Inbar Levi, Tanya Babich, Lena E Friberg, Johan W Mouton, Ursula Theuretzbacher, Leonard Leibovici

	Colistin (n=198)	Colistin and meropenem (n=208)	RR (95% CI) for outcome with combination*	p value
Primary outcome				
Clinical failure at day 14	156 (79%)	152 (73%)	0·93 (0·83–1·03)	0·172
Secondary outcomes				
28-day mortality	86 (43%)	94 (45%)	1·03 (0·84–1·28)	0·781
Disposition at day 28	..	..	..	0·550
Dead	86 (43%)	94 (45%)	..	..
Alive, not discharged	60 (30%)	70 (34%)	..	..
Alive, discharged home	30 (15%)	22 (11%)	..	..
Alive, discharged to chronic care	22 (11%)	22 (11%)	..	..
14-day mortality	64 (32%)	70 (34%)	1·04 (0·79–1·37)	0·786
Failure with modification†	171 (86%)	177 (85%)	0·99 (0·91–1·07)	0·724
Microbiological failure	62 (31%)	73 (35%)	1·1 (0·84–1·44)	0·489

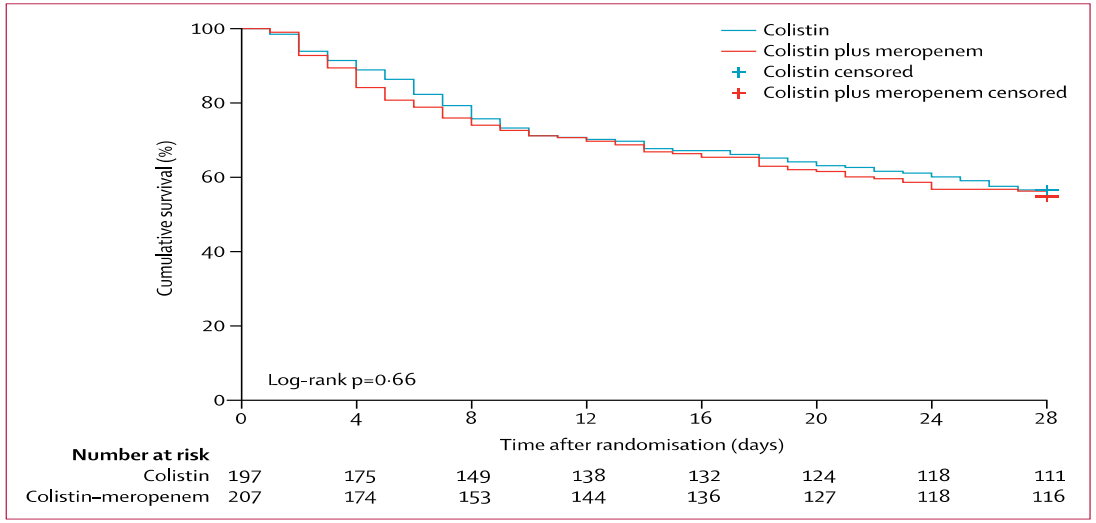


Figure 2: **Survival analysis to day 28 after randomisation**

Lancet Infec Dis 2018

Summary of RCTs

- The majority of participants had HAP/VAP or BSIs caused by CRAB
- The all-cause mortality rate was unacceptably high ranging from 38% to 63.6%
- None of the combinations was associated with better survival.
- No differences were documented regarding development of resistance.

Summary of RCTs

- The two largest studies (AIDA, Italian) do not support the use of colistine/ rifampin or colistine/meropenem.
- One study, however, showed better clinical response with colistin plus high-dose ampicillin/sulbactam and three studies showed better microbiologic response with colistin plus rifampin or fosfomycin.

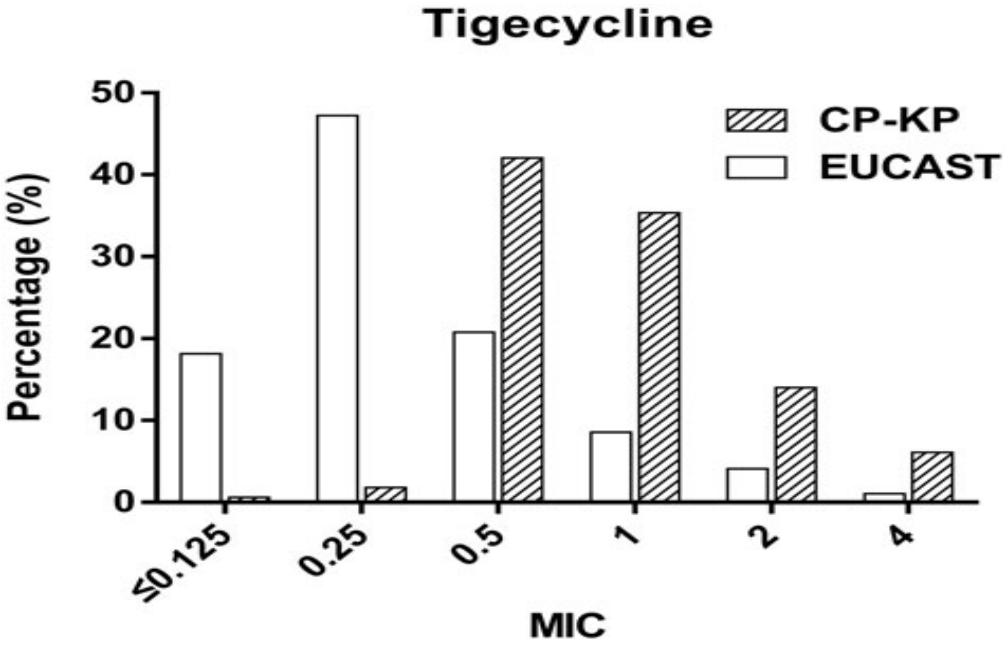
Case 3 Contn/d

- After susceptibility testing was available, Ceftazidime/avibactam was discontinued and tigecycline was added

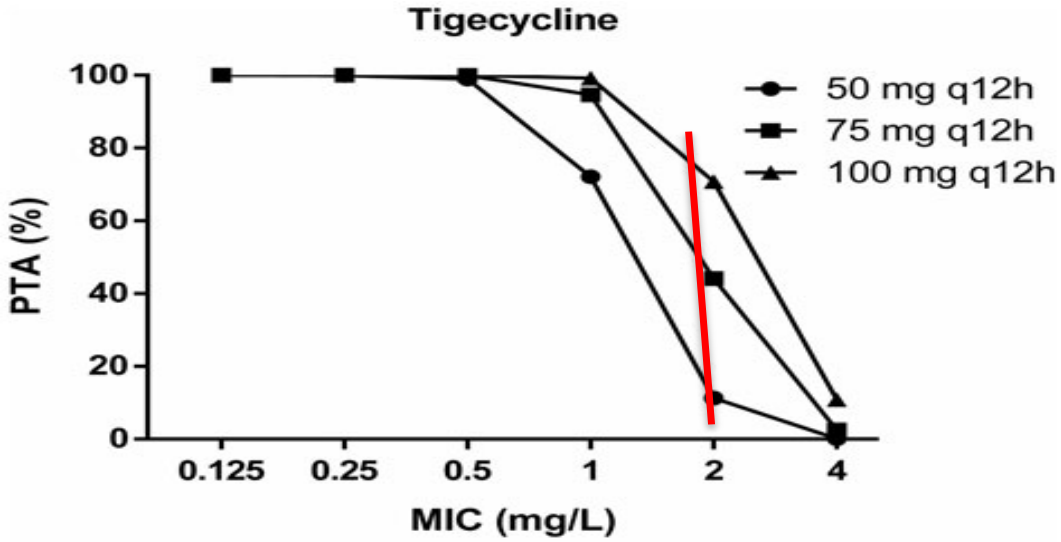
- Tigecycline 200mg as loading dose, followed by 100mg q 12hrs

Use of Monte Carlo simulation to evaluate the efficacy of tigecycline and minocycline for the treatment of pneumonia due to carbapenemase-producing Klebsiella pneumoniae

Wentao Ni, Guobao Li, Jin Zhao, Junchang Cui, Rui Wang, Zhancheng Gao & Youning Liu

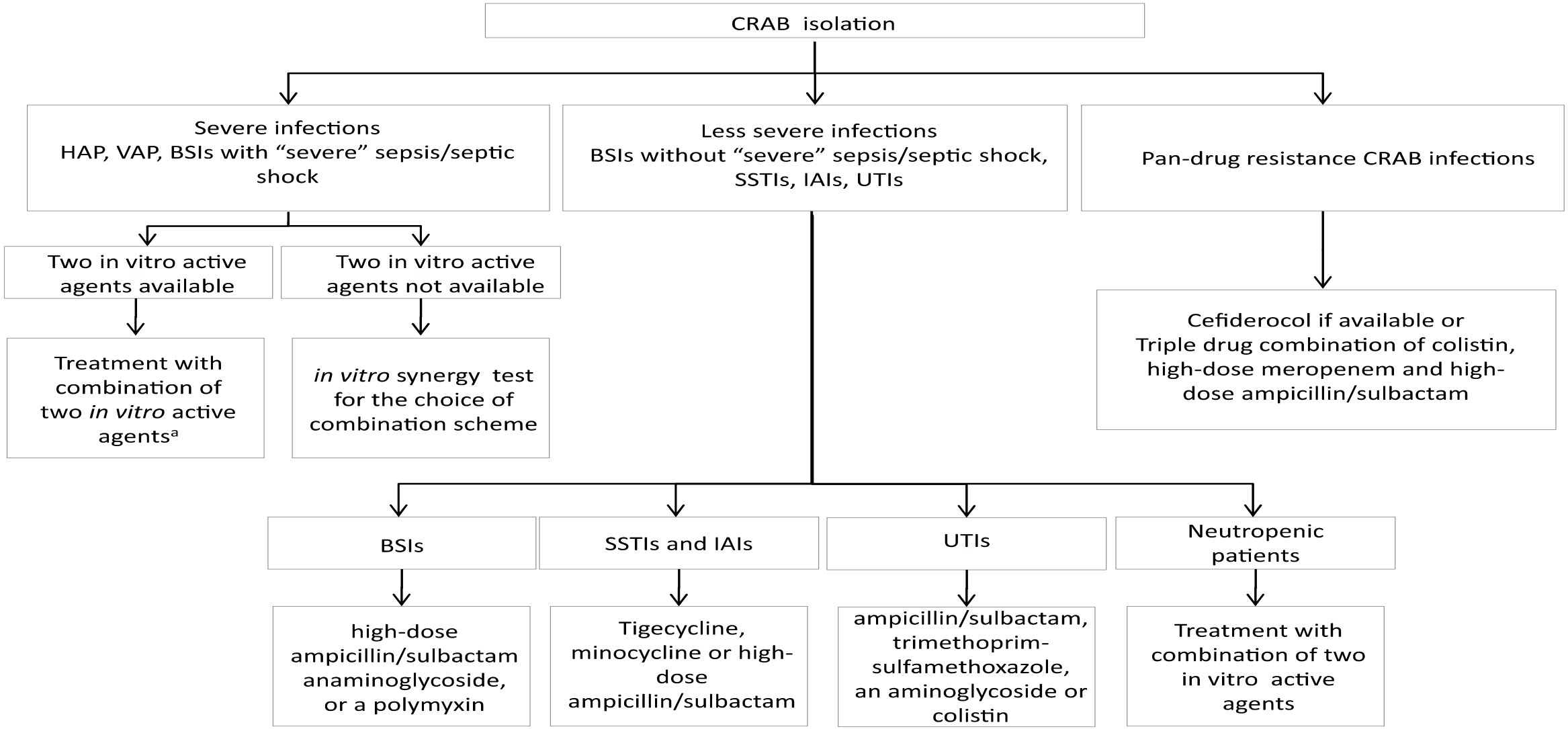


MIC distributions of 164 CP-KP strains And KP from EUCAST MIC distribution



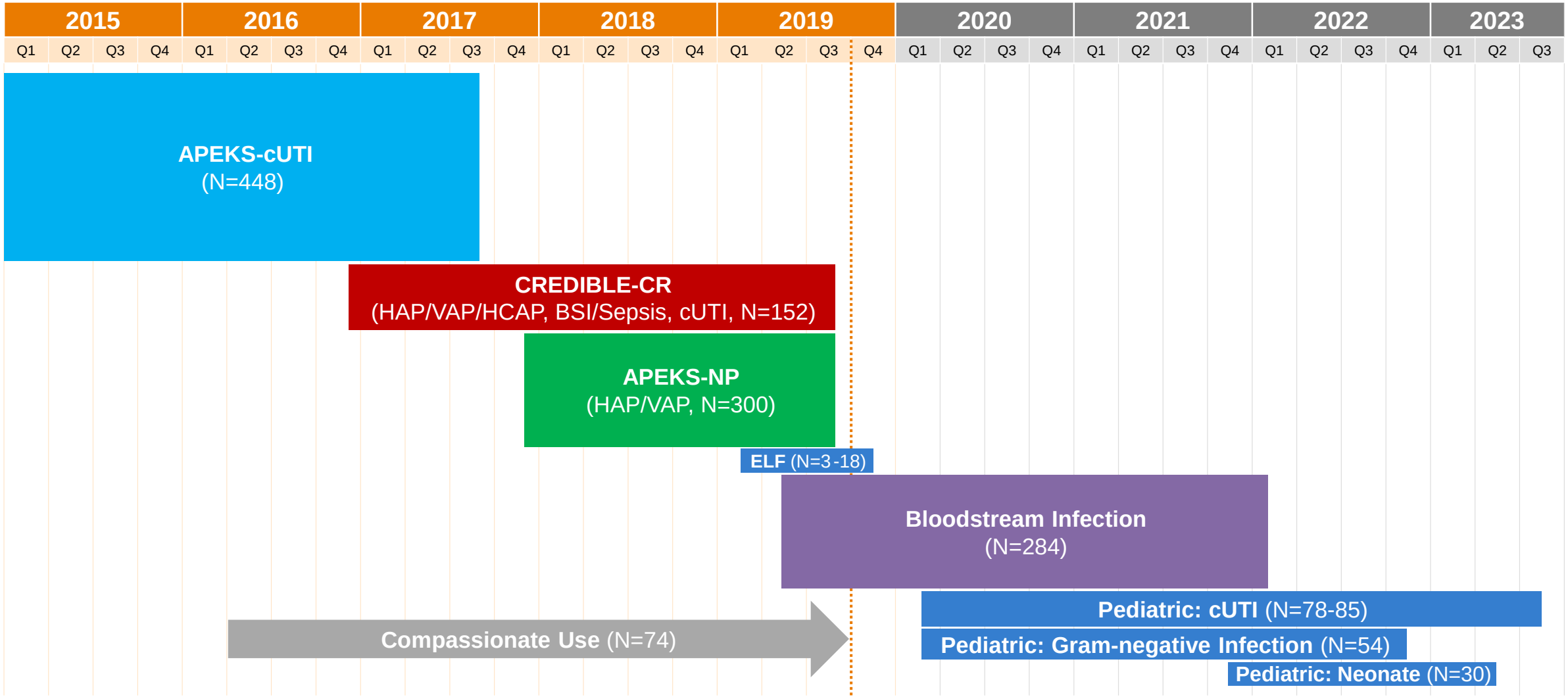
PTA (*f*AUC/MIC >0.9) 10,000 simulated pts given tigecycline at different dosages

doi.org/10.1080/23744235.2018.1423703

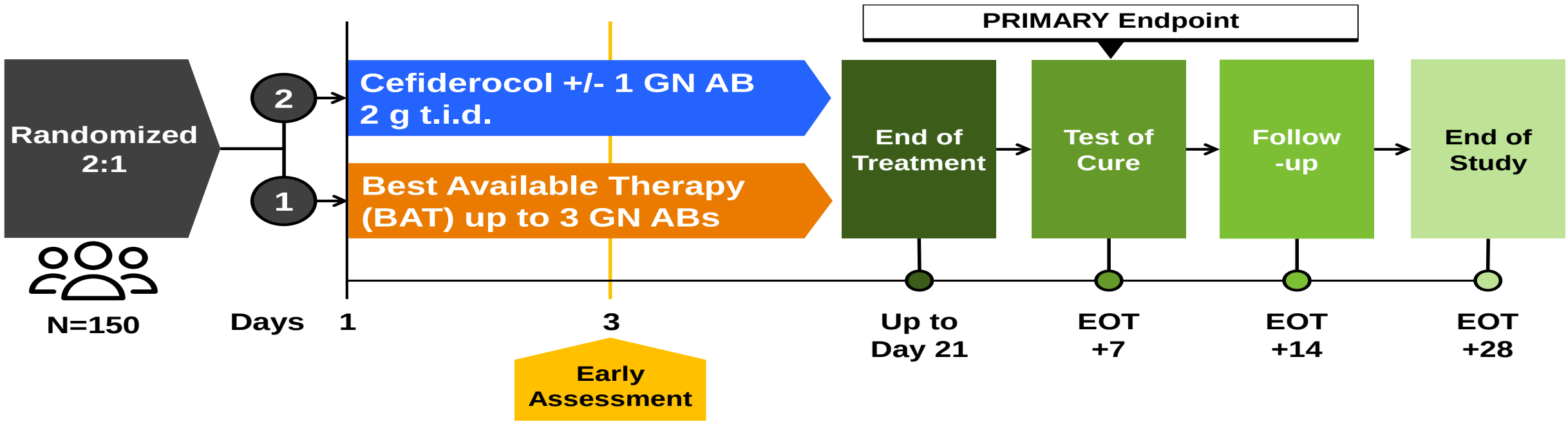


Piperaki E Clin Microb Infect doi.org/10.1016/j.cmi.2019.03.014

Planned and Ongoing Studies of Cefiderocol

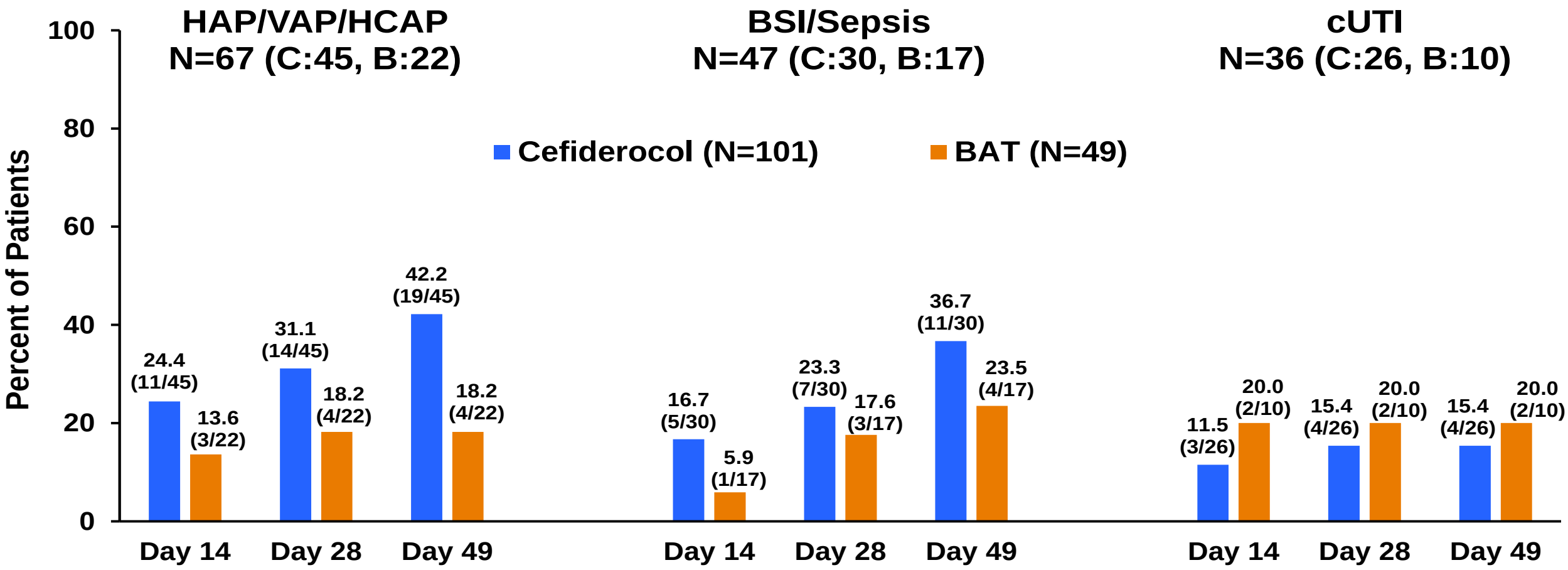


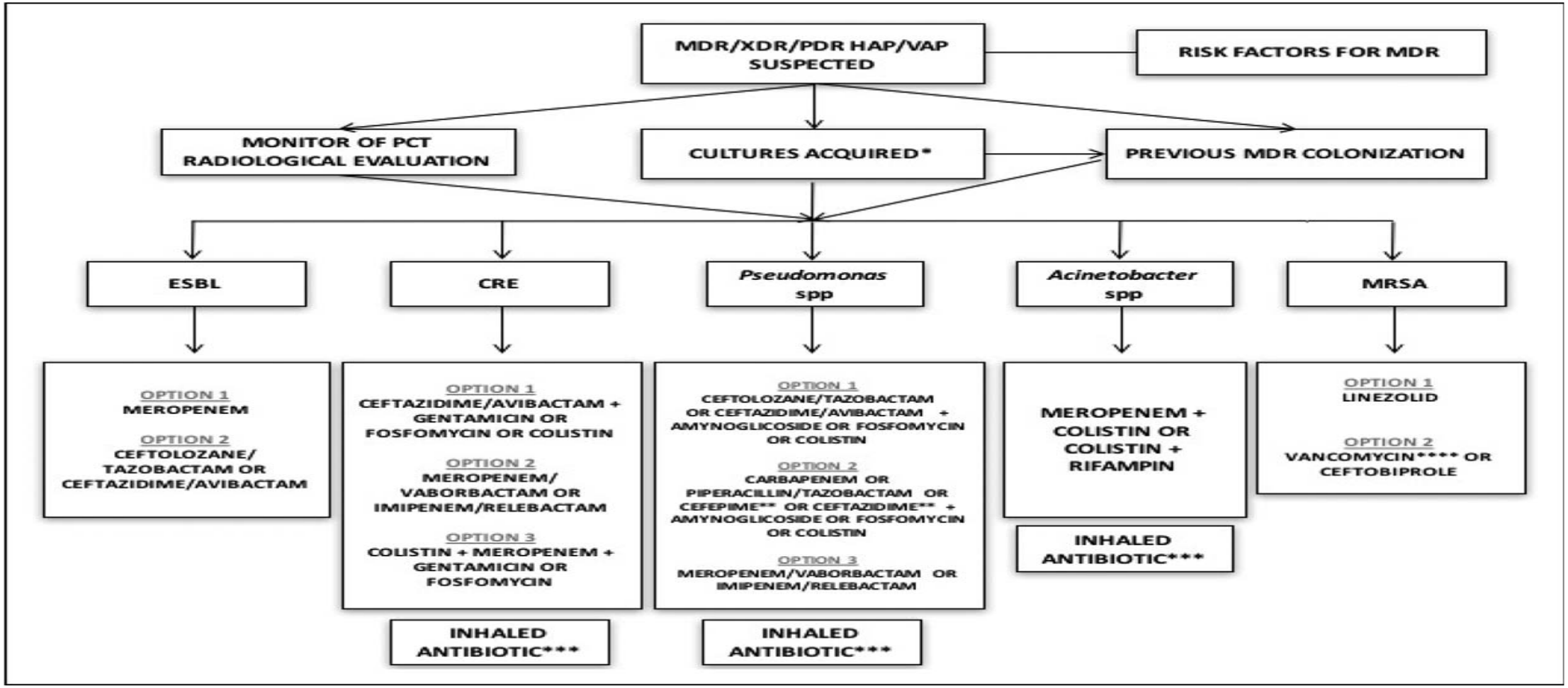
Cefiderocol vs BAT



- **Primary Endpoint at Test of Cure**
  - HAP/VAP/HCAP and Bloodstream Infections/Sepsis – Clinical outcome
  - cUTI – Microbiological outcome

Cefiderocol vs BAT



Proposed Algorithm for the Management of MDRO Infections

Bassetti et al Curr Opin Crit Care 2018, 24:385 – 393