Curriculum Vitae

Birth : Jakarta

Graduates

MD : FKUI 1994

Internist : FKUI 2003

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PhD : FKUI 2014

Position:

Medical Staff Department of Internal Medicine
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MDR Gram Negative treatment: the role of New BL-BLI

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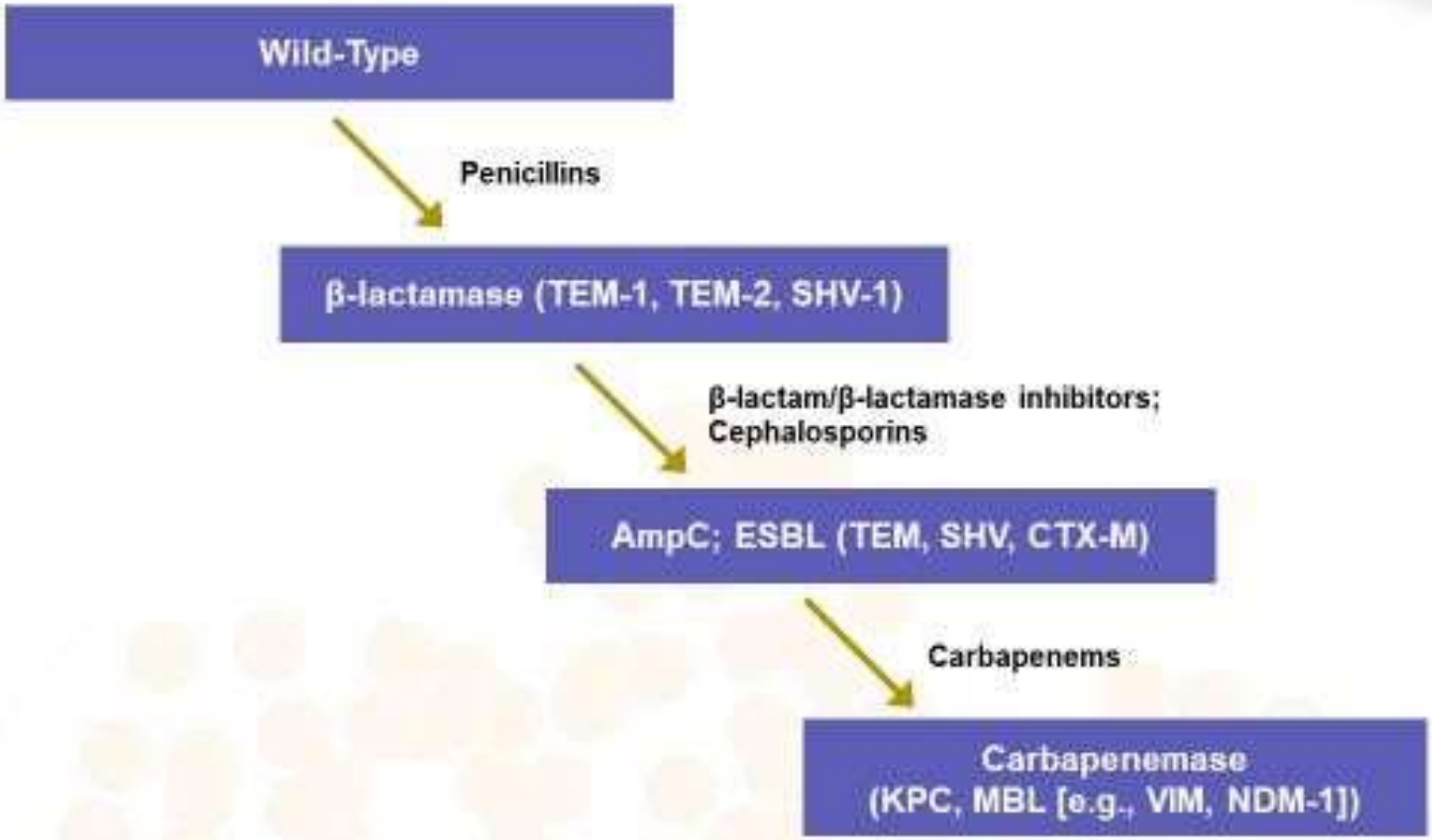
Antibiotic Resistance

An Example of Resistance Evolution[1,2]

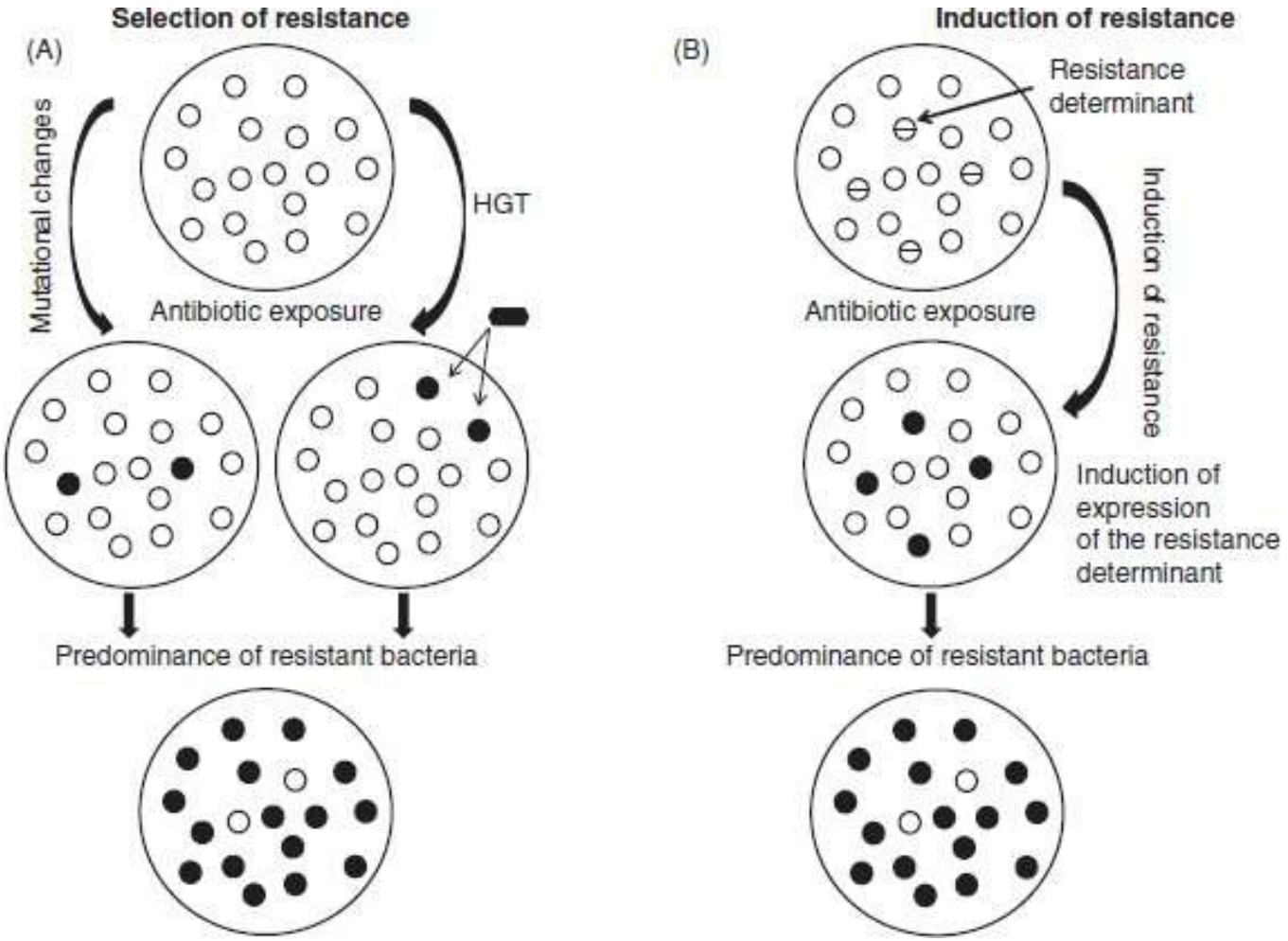


ESBL=extended-spectrum β-lactamase; KPC=Klebsiella pneumoniae carbapenemase; MBL=metallo-β-lactamase; TEM-1,TEM-2, SHV-1, TEM, SHV, CTX-M=types of β-lactamases.

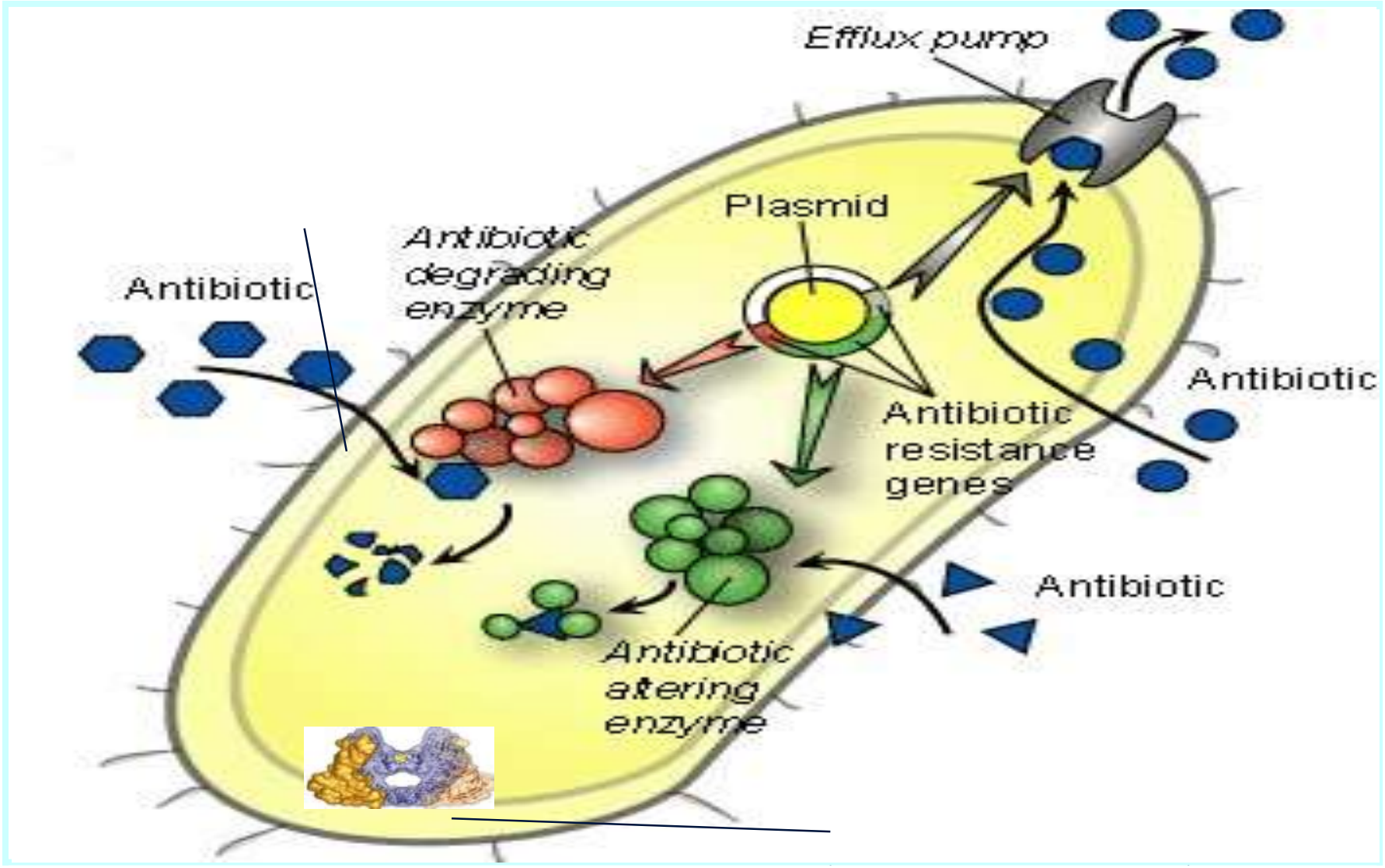
1. Originally published in Burgess DS, Rapp RP. *Am J Health-Syst Pharm*. 2008;65 (suppl 2):S4-S15.

2. Yong D, et al. *Antimicrob Agents Chemother*. 2009;53:5046-5054.

Selection and Induction as Mechanism to Resistance



Mechanisms Of Antibiotic Resistance



Clinically relevant Mechanism of Resistance in Gram negative Bacteria

	Enterobacteriaceae	*Pseudomonas aeruginosa*	*Acinetobacter*	*Staphylococcus aureus*
AmpC β-lactamases	■	■	■	
ESBL	■			
Carbapenemases	■	■	■	
DNA gyrase/ topoisomerase mutations	■	■	■	■
Aminoglycoside-modifying enzymes	■	■	■	
Multidrug efflux pumps		■	■	
Porin mutations		■	■	
Altered penicillin-binding protein			■	■
Penicillinase				■

ESBL, extended-spectrum β-lactamase

Adapted from references 9-12.

What is a Multiresistant (MDR) Gram-negative pathogen?

Consensus Definition:

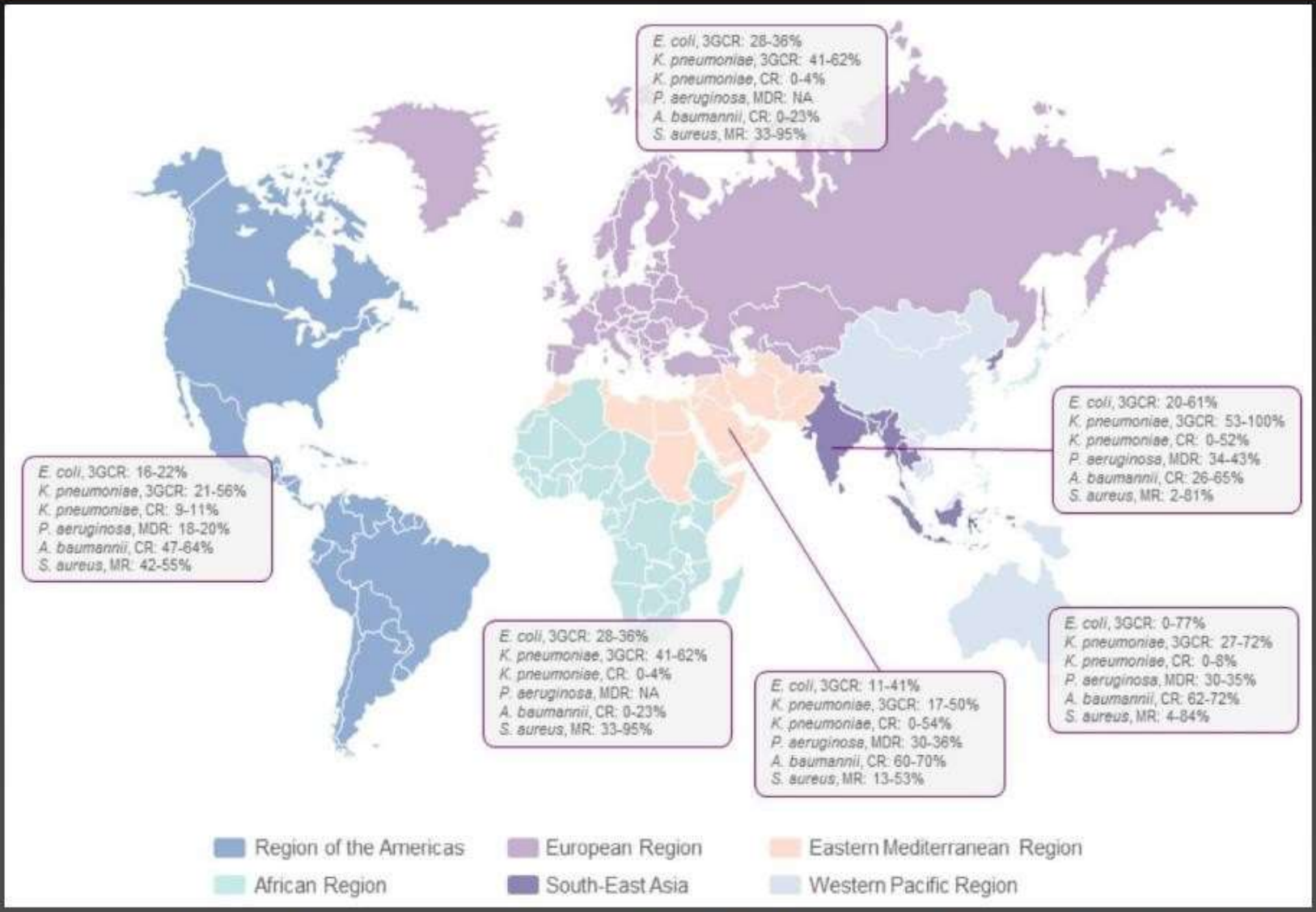
Resistant to at least one (1) antimicrobial in 3 or more antimicrobial classes

Extensively Drug-Resistant (XDR): Non-susceptible **to all** but **one or two** antimicrobial categories (usually colistin and/or tigecycline)

Pandrug-Resistant (PDR): Non-susceptible **to all** agents in all antimicrobial categories

Magiorakos et al CMI 2012

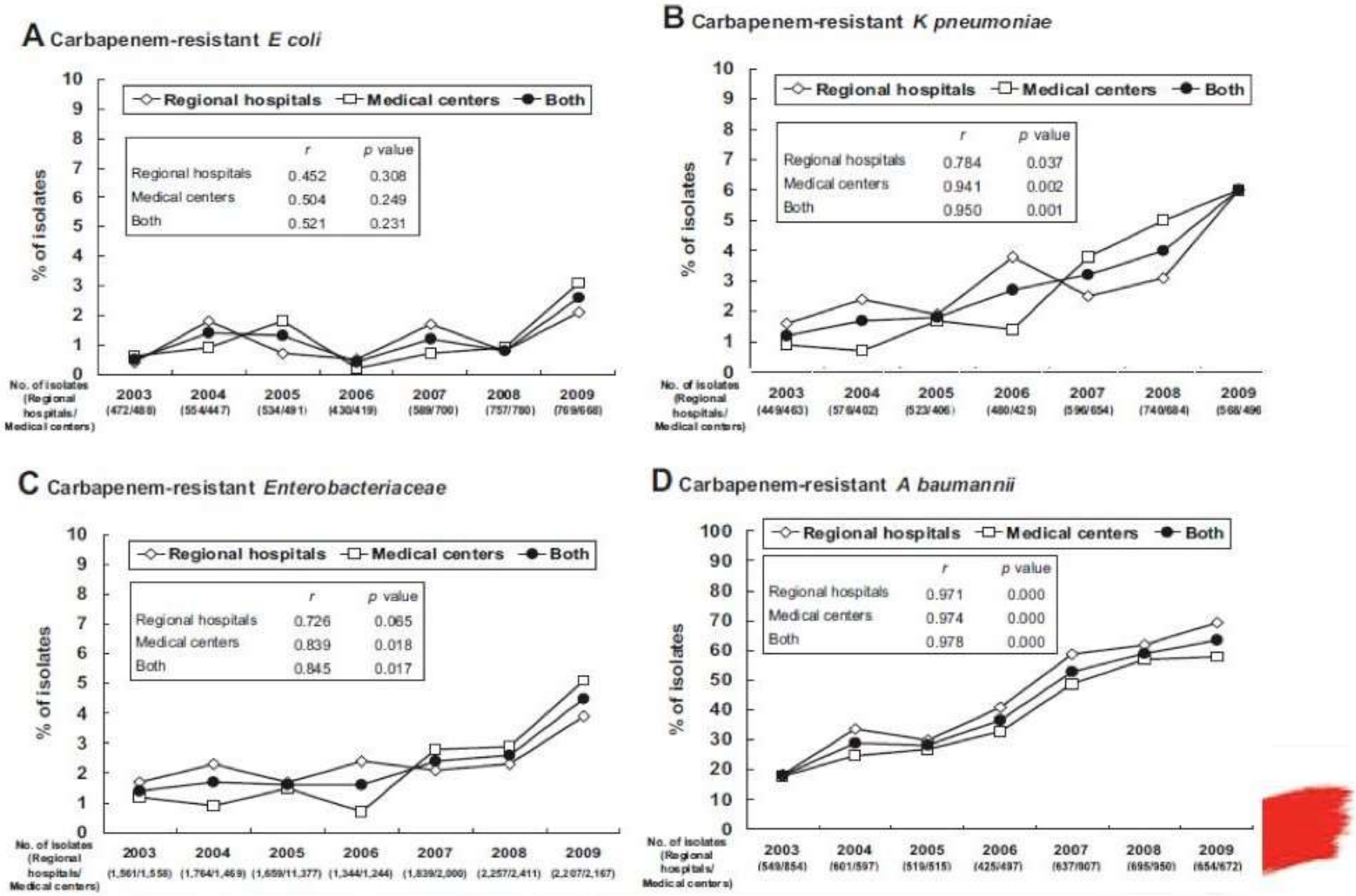
Epidemiology of MDR worldwide



Timsit JF, Bassetti M et al. *Intensive Care Med.* 2019 ;**45**(2):172-189. doi: 10.1007/s00134-019-05520-5.

Increasing trends in the rates of Carbapenem Resistant Organisms

Data from the Taiwan Nosocomial Infection Surveillance system, 2003-2009



S.-H. Tseng et al. Journal of Microbiology, Immunology and Infection (2011) 44, 157e165

Proportion of Resistance towards Cefotaxime January 2008 – December 2022 (Cont.)

Periods	*K.pneumoniae (%R)*	*E.coli (%R)*	*P. mirabilis (%R)*	*K.oxytoca (%R)*
2015 (July-December)	54	56	4	53
2016 (January-June)	61	57	15	54
2016 (July-December)	64	59	53	28
2017 (January-June)	66	59	63	25
2017 (July-December)	66	63	53	29
2018 (January-June)	66	64	66	24
2018 (July-December)	72	66	68	38
2019 (January-June)	67	61	31	66
2019 (July-December)	64	57	22	59
2020 (January-June)	64	59	14	62
2020 (July-December)	68	64	26	68
2021 (January-June)	70	65	22	63
2021 (July-December)	69	64	26	65
2022 (January-June)	68	64	20	69
2022 (July-December)	72	65	28	68

Antibiotics Susceptibility Profile of Gram-Negative Bacteria (%S)

Antibiotic name	Number	%S
Colistin	221	81.45
Meropenem	6740	67.02
Fosfomycin	1737	65.34
Amikacin	6137	61.90
Doripenem	5212	59.54
Imipenem	6935	57.16
Cefoperazone/Sulbactam	6064	56.99
Gentamicin	6948	54.50
Piperacillin/Tazobactam	6950	53.25
Levofloxacin	5249	47.46
Ceftazidime	6952	46.19
Tetracycline	6020	46.01
Chloramphenicol	5453	45.08
Cefepime	6815	44.71
Trimethoprim/Sulfamethoxazole	201	38.81

Antibiotic name	Number	%S
Aztreonam	6896	37.41
Nitrofurantoin	1738	36.54
Cefoperazone	6938	34.43
Ciprofloxacin	6698	34.22
Pipemidic acid	438	33.79
Amoxicillin/Clavulanic acid	6019	33.19
Neomycin	579	31.09
Kanamycin	6937	29.97
Ceftriaxone	6945	28.35
Nalidixic acid	1743	27.83
Tigecycline	6883	27.63
Cefotaxime	6947	19.22
Moxifloxacin	190	18.42
Erythromycin	11	18.18
Cephalothin	5887	14.66

Classification of Microorganism Producing Carbapenemases

Ambler class	Enzyme	Function	Known organisms
A	KPC[1]	Hydrolyzes all β-lactam antibiotics; inhibited by clavulanate	*K pneumoniae,* Enterobacteriaceae
B	MBLs[2] (NDM, IMP, VIM, GIM, SPM)	Hydrolyze all β-lactams except aztreonam; may be inhibited by clavulanate; require zinc for enzymatic activity; inhibited by EDTA	*P aeruginosa, Acinetobacter* spp, Enterobacteriaceae
D	OXA	Oxacillin hydrolyzing; less able to hydrolyze carbapenems	*P aeruginosa, A baumannii,* Enterobacteriaceae

Ambler classification of β-lactamases

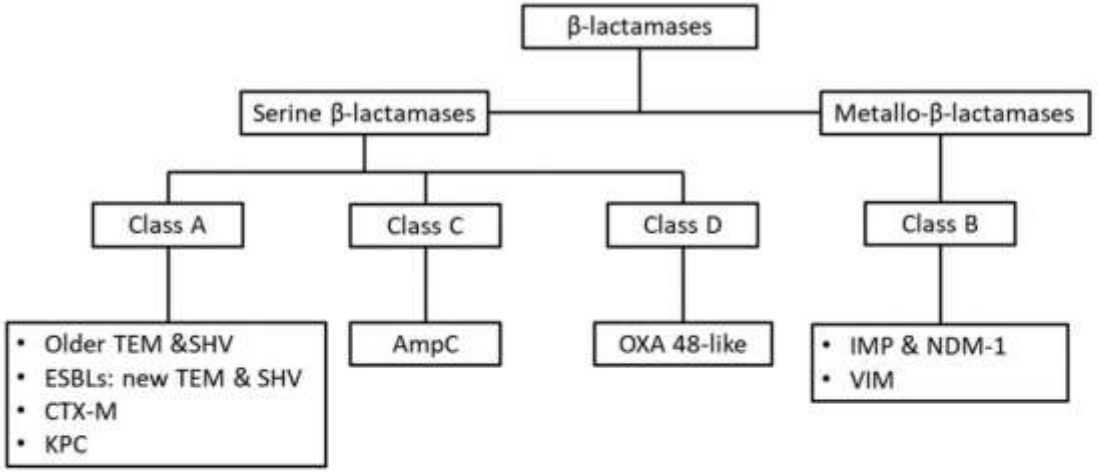


Figure 1. The Ambler classification of β-lactamases, which is based on each enzyme's primary protein structure. The active site of enzymes of Classes A, C, D contains a serine residue, which is necessary for the hydrolysis of the beta-lactam ring, while enzymes of Class B require zinc ion cofactor in order to function (thus termed metallo-β-lactamases) [3,4]. Abbreviations: ESBL: extended spectrum β-lactamase; TEM, Temoniera; SHV, sulfhydryl variable; CTX-M, Cefotaxime β-lactamase; KPC, *Klebsiella pneumoniae* Carbapenemase; OXA, oxacillinase; IMP, Imipenemase type carbapenemase; NDM-1, New Delhi metallo-β-lactamase; VIM, Verona integron-encoded metallo-β-lactamase.

Carbapenem Resistant Gram-Negative Microorganisms Treatment options

Pseudomonas aeruginosa (MBL, KPC, efflux pumps, porin loss...)	*Enterobacteriaceae* (VIM, KPC, NDM, OXA-48..)	*Acinetobacter baumanii* (OXA,MBL,efflux pumps..
• Colistin • Aminoglycoside • Fosfomycin • Aztreonam	• Colistin • Aminoglycoside • Tigecycline • Fosfomycin	• Colistin • Tigecycline • Aminoglycoside • Sulbactam
FQ? Ceftolozane/tazo?	FQ? Cotrimoxazole? Chloramphenicol? Tetracyclines?	FQ? Cotrimoxazole? Tetracyclines?

In-vitro antibiotic synergistic study to MDRO

- The most studied combination is of polymyxins (most often colistin) with b-lactams, mostly carbapenems
- Checkerboard and time kill studies were most often used with checkerboard reported lower rate of synergism
- In all 3 bacteria the combination was synergisitic with greater effect shown in Acinetobacter (77%)
- Synergistic effect remained for Colistin S and carbepenem R strains (55-71%)
- In resistant to both strains the cidal activity increased form 14% to 43% with the combination
- Doripenem had the higher overall synergistic effect followed by meropenem and imipenem
- In vitro resistance development was also reduced

gatto MH et al Principles and Practice Clin Res 2015, Zusman et al AAC 2013, March G et al J Microbiol Methods 2015

In-vitro antibiotic synergistic study to MDRO

- Combination of polymyxins with other b-lactams resulted in low synergistic rates
- Tigecycline had to be tested in doses equivalent to 400mg/d to show synergism
- Colistin with rifampin, vancomycin or daptomycin showed synergism against Acinetobacter
- Colistin with levofloxacin had 90% synergistic effect against Pseudomonas and 84% against Acinetobacter
- Colistin with fosfomycin was synergistic against NDM-1KP

Rigatto MH et al, Principles and Practice Clin Res 2015
Zusman et al AAC, 2013
March G et al, J Microbiol Methods 2015, Lin et al Ebiomed 2015

Combination Treatment for KPC

		Benefit from combination
Zarkotou CMI 2011	35 BSI	Y: Significant reduction in mortality 46 vs 0%
Qureshi AAC 2012	41 BSI	Y: Significant reduction in mortality 52 vs 13%
Tumbarello CID 2012	125 BSI	Y: Significant reduction in mortality 54%vs34%
Daikos AAC 2014	205 BSI	Y: Significant reduction in mortality 44 vs 27%. In those at high risk of death
Tofas IJAA 2016	50 BSI	Neutropenics.Y: Reduction in mortality
Gutiérrez-Gutiérrez Lancet Infect Dis in press	437 BSI	Reduction in mortality only in patients at a high risk of death
De Oliveira CMI 2015	118 pts 78 BSI	No difference in outcome
Gomez-Simmonds AAC2016	141 BSI	No difference in mortality (33%)

Combinations : mostly tigecycline +colistin, carbapenem + colistin

Combination treatment for MDR Acinetobacter

STUDY	TYPE	AGENTS	No pts (VAP mostly)	28 DAYS-MORTALITY (COL VS COMBI)	PATHOGEN ERADICATION
Shields 2012	Retrospective	COL VS COL +CARBA	41	46% Combination=factor of survival	
Simsek 2012	Retrospective, case-control	COL VS COL +RIFAMPIN	51	40 VS 47%	NA
Aydemir 2013	Randomized, open	COL VS COL+RIFAMPIN	43	67 VS 72%	59 VS 71%
Durante – Mangoni 2013	Randomized, open	COL VS COL + RIFAMPIN	210	42.9 VS 43.3 %	36 VS 60%
Kalin 2013	Retrospective	COL VS COL +SULBACTAM	89	52 VS 73%	72 VS 85%
Sirijatuphat 2014	Randomized, open	COL vs COL+FOSFO	94	57vs 47%	80vs100%

STUDY	TYPE	AGENTS	No pts	effect
Batirel 2014	Retrospective	COL vs COL +Carba or sulbactam or tigecycline	250	Lower 14-day mortality and higher microbiological eradication in combination
Lopez-Cortez 2014	Prospective observational	COL or Carba vs COL+tigecycline	101 (VAP)	No difference in 30-day mortality
Rigatto 2015	Cohort study	COL vs COL + R in vitro agent	101	Lower mortality with combination
Cheng 2015	Retrospective	COL+TIGE VS COL +CARBA	55 BSI	Combination of COL+CARBA had lower mortality (15 vs 35%).
Garnacho-Montero 2013	Retrospective	COL vs COL +VANCO	57 VAP,BSI	No difference in mortality and clinical cure, increased nephrotoxicity
Petrosillo 2014	Retrospective	COL OR COL +GLYCOPEPTIDES	184 VAP,BSI	Presence of glycopeptides >5 days had a protective effect

Monotherapy vs Combination therapy in Pseudomonas Bacteremia : Clinical Evidence

Micek et al, AAC 2005	Retrospective cohort study No=305, **non MDR** 1997-2002	Overall mortality=21% Inappropriate RX increased mortality (30.7vs17.8%). Combination initial treatment Rx increased the likelihood of appropriate RX
Chamot et al, AAC 2003	Retrospective cohort study No=115, **non MDR**	Overall mortality=39.4% Adequate initial combination treatment related to decreased 30-day mortality
Bowers et al, AAC 2013	Retrospective cohort study No=384**, non MDR** 2002-2011	No difference in mortality between monotherapy and combination therapy. Higher mortality for inappropriate empirical treatment 43.8% vs21.5%
Vardakas et al, IJAA 2013	Metanalysis. 19(9 RCTs) studies. No=1721 non MDR	No difference in mortality between mono- and combination therapy in bacteremia and severe infection
Pena et al, CID 2013	**Post hoc analysis from a prospective cohort. No=593 30% MDR**	**No differences between adequate monotherapy and combination therapy (b-lactam +aminoglycosides or FQ) in mortality**

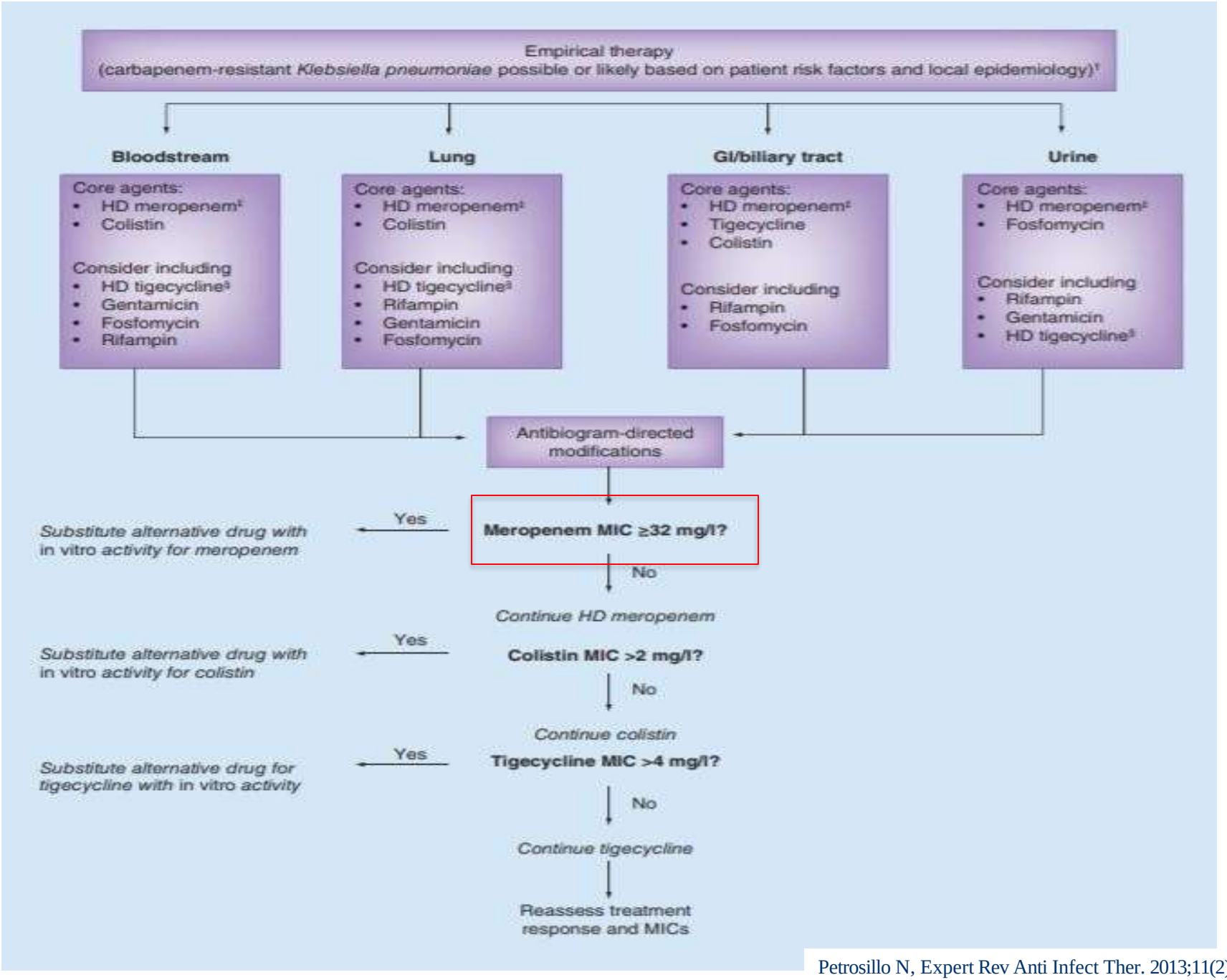
Potential Treatment Algorithm for Carbapenem-Resistant KPC-Producing *Klebsiella pneumoniae**

Infection Source	Empiric Treatment: Core Drugs	Empiric Treatment: Possible Adjunct Drugs	Antimicrobial Susceptibility Directed Treatment Considerations
Bloodstream	• High-dose meropenem or doripenem • And polymyxin B	• Aminoglycoside • Tigecycline • Fosfomycin • Rifampin	Meropenem/doripenem: • MIC ≤16 μg/mL continue high-dose meropenem/ doripenem • MIC >16 μg/mL consider alternative in vitro active antimicrobial[a] Polymyxin B/colistin: • MIC ≤ 2 μg/mL continue polymyxin B/colistin[b,c] • MIC >2 μg/mL consider alternative in vitro active antimicrobial If both meropenem/doripenem MIC (>16 μg/mL) and polymyxin B/colistin MIC (>2 μg/mL), then consider a high-dose tigecycline-based regimen or a dual dual carbapenem-based regimen[d,e] If pan-drug-resistant infection, select case-reports support dual carbapenem-based regimen[e] Tigecycline: • MIC ≤1 μg/mL consider tigecycline[d] • MIC >1 μg/mL consider alternative in vitro active antimicrobial Fosfomycin[f]: • MIC ≤32 μg/mL consider fosfomycin • MIC >32 μg/mL consider alternative in vitro active antimicrobial Amioglycoside: • MIC ≤2 μg/mL (Gentamicin/ Tobramycin) or ≤4 μg/mL (Amikacin) consider aminoglycoside • MIC >2 (Gentamicin/ Tobramycin) or >4 μg/mL (Amikacin) consider alternative in vitro active antimicrobial
Lung	• High-dose meropenem or doripenem • And polymyxin B	• Tigecycline • Aminoglycoside • Fosfomycin • Rifampin	
Gastrointestinal/biliary tract	• High-dose meropenem or doripenem • And polymyxin B • And high-dose tigecycline	• Fosfomycin • Rifampin	
Urine	• High-dose meropenem or doripenem • And fosfomycin[g] • Or aminoglycoside[g]	• Colistin • Aminoglycoside	

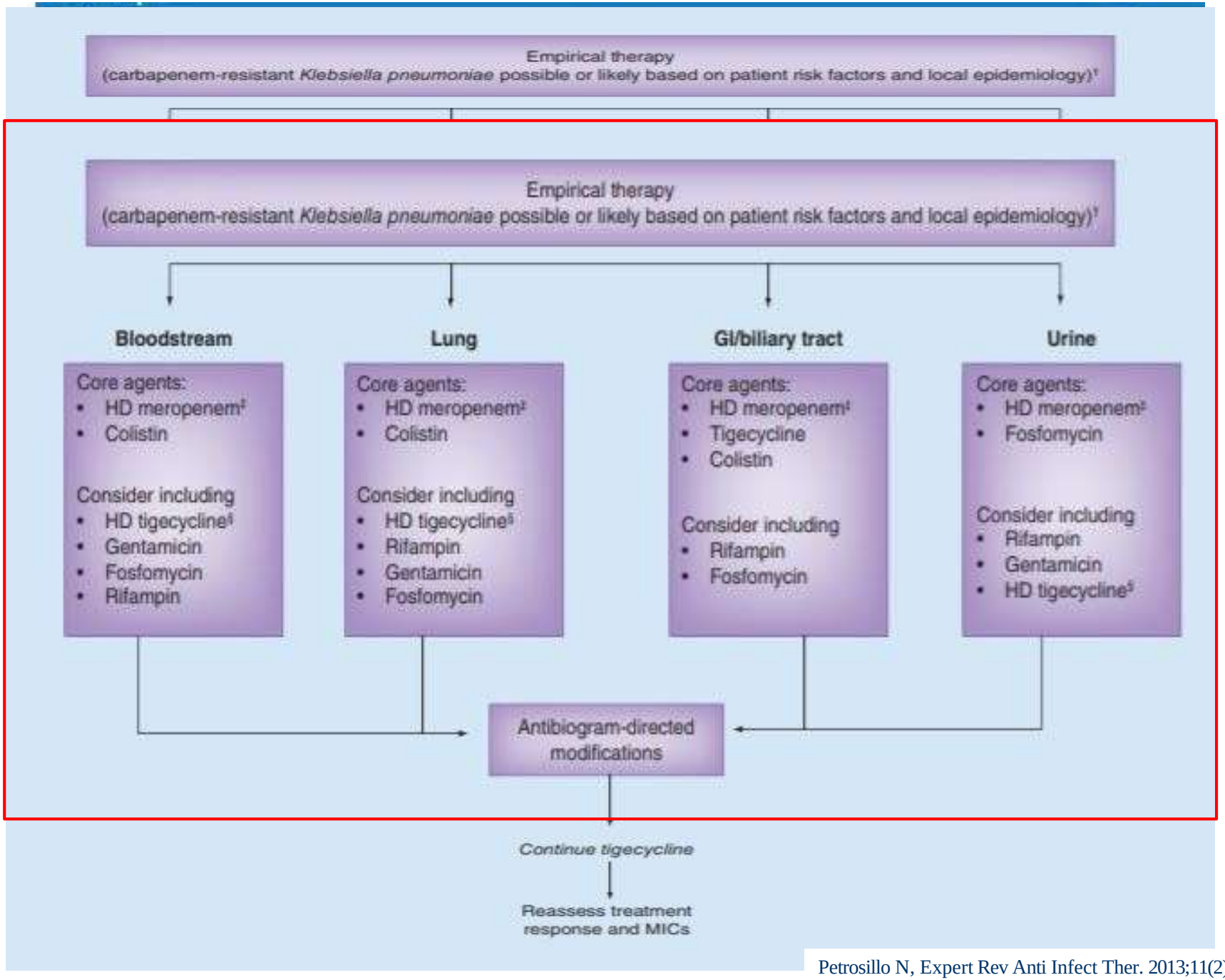
Optimizing Carbapenem Usage for Carbapenemase Producing K. pneumonia

Drug	PK:PD parameter	V_d (l) Typical loading dose†	Maintenance dose	Ref.
Doripenem	40% *f*Time > MIC	16.8	1000–2000 mg every 8 h	[111,112]
"	"	1000–2000 mg	4-h infusion	"
"	"	"	CrCL >50 ml/min: standard dose	"
"	"	"	CrCL 26–50: reduce dose by 50%	"
"	"	"	CrCL 26 ml/min or HD/CVVHD: Use renally-adjusted dose with intermittent infusion	"
Meropenem	40% *f*Time > MIC	15–20	2000 mg every 8 h	[69]
"	"	2000 mg	4-h infusion	"
Colistin‡	*f*AUC:MIC 25–50	45.1	Daily dose of CBA (mg) colistin = C_p § (1.50 × CrCL × 30)	[79]
Tigecycline	*f*AUC:MIC 1	490–700	50–100 mg every 12 h	[87,90]
"	"	100–200 mg	'High-dose' therapy 200-mg loading dose, then 100 mg once daily	"
Gentamicin	*f*AUC:MIC 156	17.5	5 mg/kg/day for MIC <1; 7 mg/kg for MIC >2	[92]
"	"	No loading dose ecommendation	Dose adjustment for renal dysfunction is guided by plasma concentration monitoring	"
Fosfomycin	60% fTime > MIC	17–25 No loading dose recommendation	8000 mg every 12 h	[95]

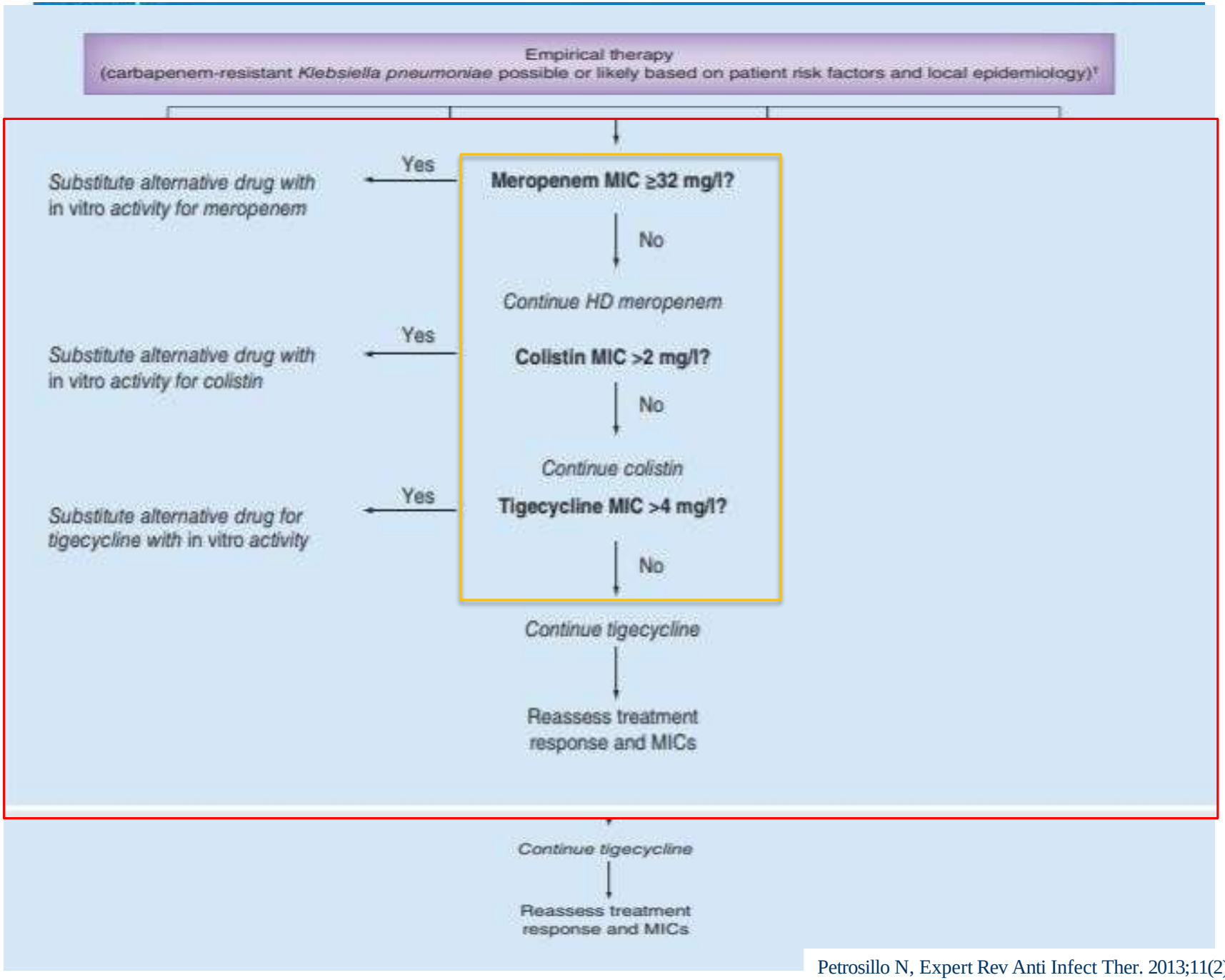
Petrosillo N, Expert Rev Anti Infect Ther. 2013;11(2):159-177.



Petrosillo N, Expert Rev Anti Infect Ther. 2013;11(2):159-177



Petrosillo N, Expert Rev Anti Infect Ther. 2013;11(2):159-177



Petrosillo N, Expert Rev Anti Infect Ther. 2013;11(2):159-177

Polymixin/Colistin

- Polymixin E (Colistin), Polymixin E
- Praparation : Colismethate : pro drug of Colistin, Polimyxin
  Oral form can't be used for systemic treatment as can't be absorb in GI
- Indication : **Definite** treatment of MDR/XDR Pseudomonas aeruginosa and Acinetobacter baumanii
  in combination with Group 2 Carbapenem, PIPTAZO, Fosfomycin or Aminoglycoside
- Dosage : 0.75-1.25 mg/kg (7,500-12,500 U/kg) iv drip q 12 h

New Agents against MDR Pseudomonas aeruginosa and Acinetobacter baumanii

Type of Resistance	Common Organisms	Recommended Treatment	Comments
AmpC β-lactamase	*Enterobacter cloacae* and other Enterobacteriaceae	Any carbapenem or cefepime (Maxipime, Hospira)	TMP-SMX, quinolone; tigecycline also may be effective
ESBL	*Klebsiella pneumoniae* and other Enterobacteriaceae	Any carbapenem	TMP-SMX, quinolone; tigecycline also may be effective
Carbapenemase	*K. pneumoniae* and other Enterobacteriaceae	Ceftazidime-avibactam	Meropenem or tigecycline (Tygacil, Pfizer) + polymyxin E (colistin)
Alteration of penicillin-binding protein	MRSA	Vancomycin	Daptomycin, linezolid, TMP-SMX, and ceftaroline are alternatives
Mutation of DNA gyrase and topoisomerase	*Enterococcus faecium* (VRE)	Linezolid (Zyvox, Pfizer) or daptomycin	Tigecycline may be an alternative agent
Decreased permeability plus increased efflux + de-repressed AmpC	*Pseudomonas aeruginosa, Acinetobacter baumannii*	Ceftolozane-tazobactam	Tigecycline may be effective against certain strains of *A. baumannii*
Aminoglycoside-modifying enzymes	*P. aeruginosa, A. baumannii*	Meropenem (Merrem I.V., AstraZeneca), imipenem (Primaxin I.V., Merck), piperacillin-tazobactam (Zosyn, Pfizer), or cefepime	

ESBL, extended-spectrum β-lactamase; **MDR,** multidrug-resistant; **MRSA,** methicillin-resistant *Staphylococcus aureus*; **TMP-SMX,** trimethoprim-sulfamethoxazole; **VRE,** vancomycin-resistant enterococci

Adapted from references 17 and 18.

Anti-Gram-negative activity of new antibiotics

	ESBL	CRE	MDR *P.aeruginosa*	MDR Acinetobacter
Cefiderocol	YES	KPC and NDM-1	YES	YES
Ceftolozane- Tazobactam	YES	NO	YES	NO
Ceftazidime-avibactam	YES	KPCs and OXA-48 (not active against MBLs)	YES	NO
Ceftaroline fosamil-avibactam	YES	KPCs and OXA-48 (not active against MBLs)	NO	NO
Aztreonam-avibactam	YES	MBLs such as NDM	YES	NO
Meropenem/vaborbactam	YES	KPCs	NO^	NO
Imipenem/cilastatin-relebactam	YES	KPCs and OXA-48 (not active against MBLs)	NO^	NO
Plazomicin	YES	most KPCs (not active against many NDMs)	NO^	NO
Eravacycline	YES	KPCs	NO	YES

^Active against P. aeruginosa, but not MDR P. aeruginosa., ESBL: extended-spectrum β-lactamases; KPC: K. pneumoniae carbapenemase; OXA: oxacillinase; MBL: metallo-β-lactamase; MDR: multidrug resistant; NDM: New Delhi metallo-beta-lactamase; CRE: carbapenemase-producing *Enterobacteriaceae*.

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Bassetti M et al. *Expert Review of Anti-infective Therapy* 2017 Jan;15(1):55-65

Avibactam: a broader spectrum of β-lactamase inhibition

		Clavulanic acid	Tazobactam	Avibactam
Class A	TEM, SHV	✓	✓	✓
	CTX-M	✗	✓	✓
	KPC	✗	✗	✓
Class B	IMP, VIM, NDM1	✗	✗	✗
Class C	AmpC	✗	✗	✓
	ACC-1, CMY-1, FOX	✗	✗	✓
Class D	OXA 48	✗	✗	✓

CTX-M, cefotaxime-β-lactamase; KPC, *K. pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; TEM, temoneira; SHV, sulfhydryl variable; VIM, Verona integron-encoded metallo-β-lactamase. Zhanel GG, et al. Drugs 2013;73:159–77; Stachyra T, et al. Anitmicrob Agents Chemother 2010;54:5132–8; Lagacé-Wiens P, et al. Core Evid 2014;9:1; Augmentin SPC;

Novel BL-BLI for MDRO

	ESBL	AmpC	KPC	OXA	MBL
Ceftolozane-tazobactam	+	+/-	-	-	-
Ceftazidime-avibactam	+	+	+	+	-
Meropenem/vaborbactam	+	+	+	-	-
Aztreonam-avibactam	+	+	+	+	+
Imipenem-relebactam	+	+	+	-	-
Meropenem/nacubactam	+	+	+	+	+

Lagace-Wiens et al. Infect Drug Res 2014;9:13-25
Castanheira et al. AAC 2012;56:4779-85

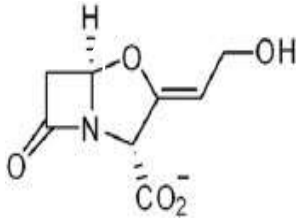
Livermore et al. AAC 2011; 55:390-4
Hong et al. Infect Drug Res 2013;6:215-23

Livermore et al. JAC 2013;68:2286-90

Avibactam: first-in-class of novel β-lactamase inhibitors

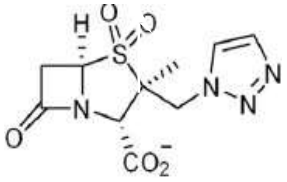
- Avibactam is a novel, first-in-class, non-β-lactam β-lactamase inhibitor from a new chemical class, diazabicyclooctane (DBOs)
- The older β-lactamase inhibitors, all structurally related to β-lactams, caused acylation & subsequent irreversible inactivation of the β-lactamase
- Avibactam differs from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

Clavulanic



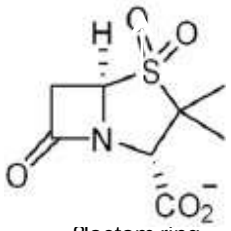
βlactam ring

Tazobactam



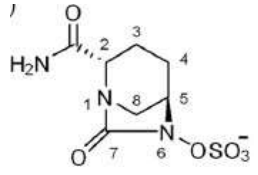
βlactam ring

Sulbactam



βlactam ring

Avibactam



Ceftazidime–avibactam Phase III clinical trial programme

Seven prospective, international, multicenter, randomized Phase III studies

RECLAIM 1, 2 and 3: Adults with cIAI	RECAPTURE 1 and 2: Adults with cUTI (including acute pyelonephritis)	REPRISE Adults with CAZ-resistant pathogens	REPROVE Adults with nosocomial pneumonia (including VAP)
• Double-blind randomization (1:1) – CAZ 2000 mg + AVI 500 mg + metronidazole 500 mg IV q8h or – MER 1000 mg IV + placebo q8h • Primary objective – RECLAIM 1 and 2: – Assess non-inferiority of CAZ–AVI re: clinical cure at TOC visit in patients with ≥1 identified pathogen (mMITT populations) – RECLAIM 3: – Proportion of patients with clinical cure at TOC visit (CE populations)	• Double-blind randomization (1:1) – CAZ 2000 mg + AVI 500 mg q8h IV or – DOR 500 mg + placebo q8h IV • Primary objective – Assess non-inferiority of CAZ–AVI on co-primary endpoints in mMITT analysis set: – Resolution of UTI-specific symptoms – Resolution/improvement of flank pain – Per-patient microbiological eradication and symptomatic resolution	• Open-label randomization (1:1) – CAZ 2000 mg + AVI 500 mg + metronidazole 500 mg q8h IV or – Best available therapy • Primary objective[4] – Estimate per-patient clinical response to CAZ–AVI and best available therapy at TOC visit in cUTI and cIAI caused by CAZ-resistant Gram-negative pathogens	• Double-blind randomization (1:1) – CAZ 2000 mg + AVI 500 mg q8h IV or – MER 1000 mg + placebo q8h IV – Plus open-label empiric linezolid + aminoglycoside • Primary objective – Assess non-inferiority of CAZ–AVI on clinical cure rate at TOC visit in cMITT and CE populations

AVI, avibactam; CAZ, ceftazidime; CE, clinically evaluable; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; DOR, doripenem; IV, intravenous; MER, meropenem; mMITT, microbiological modified intent-to-treat; TOC, test of cure; VAP, ventilator-associated pneumonia.Mazuski JE, et al. Clin Infect Dis 2016;62:1380–9; ClinicalTrials.gov. NCT01726023; Wagenlehner F, et al. Clin Infect Dis 2016;63:754–62; Carmeli Y, et al. Lancet Infect Dis 2016;16:661–73; Torres et al. Lancet Infect Dis. 2018;18(3):285–95.

Ceftazidime–avibactam trial program

Key features

- Ceftazidime–avibactam has been compared with the carbapenems for resistant Gram-negative infections in all three indications (cIAI, cUTI and HAP)
- The dosing of ceftazidime–avibactam has been consistent in all three indications in the Phase III program
- The REPRISE study is the first pathogen-directed clinical trial examining its efficacy against ceftazidime-resistant Gram-negative pathogens
- The effectiveness in RECAPTURE and REPRISE, including against ceftazidime-non-susceptible pathogens, highlights its potential clinical value as an alternative to carbapenem treatment in this setting
- The safety profile of ceftazidime–avibactam has been consistent throughout the Phase III program
- Ceftazidime–avibactam is the first to receive the fourth indication allowing its use in those patients with aerobic Gram-negative infections who have limited treatment options
- REPROVE is the first Phase III study of ceftazidime–avibactam in adults with HAP and VAP
  - It is the first randomized controlled trial to show non-inferiority, compared with a carbapenem, of a new antimicrobial therapy targeting Gram-negative pathogens in this setting

AVI, avibactam; CAZ, ceftazidime; ; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HAP, hospital-acquired pneumonia; VAP, ventilator-associated pneumonia. Zavicefta SmPC; Mazuski JE, et al. Clin Infect Dis 2016;62:1380–9; Wagenlehner FM, et al. Clin Infect Dis 2016;63:754–62; Carmeli Y, et al. Lancet Infect Dis 2016;16:661–73; Torres A, et al. Lancet Infect Dis 2018;18:285–295.

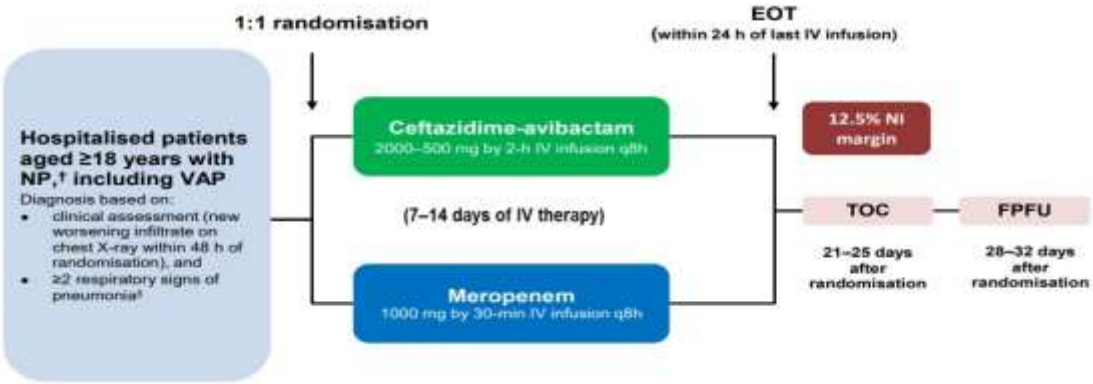
Table 3 List of major randomized, controlled clinical trials of systemic antimicrobial agents actually available for treating NP in the last 10 years

Author, year, name of the trial	Antimicrobial tested and comparator	Phase, blinded, design	Microorganism	Subject	Primary outcome	Results of primary outcome	Mortality	Comments
Freire, 2010 [76]	Tigecycline (T) Imipenem (I)	III, yes, NI	All pathogens	HAP + VAP	Clinical response in CE and c-mITT populations at TOC	c-mITT: T, 62.7%; I, 67.6% CE: T, 67.9%; I, 78.2%	T, 14.1% I, 12.2%	T was non-inferior to I for c-mITT but not the CE population due to the results in VAP. FDA warning against T use for VAP.
Rubinstein, 2011, ATTAIN 1 and 2 [60]	Telavancin (Te) Vancomycin (V)	III, yes, NI	Gram-positive	HAP	Clinical response at FU/TOC	AT: Te, 58.9%; V, 59.5% CE: Te, 82.4%; V, 80.7%	Te, 21.5% V, 16.6%	Increases in serum creatinine level were more common in the telavancin group.
Kollef, 2012 [78]	Doripenem (D), 7 days Imipenem (I), 10 days	IV, yes, NI	All pathogens	VAP	Clinical cure at EOT (day 10) in the MITT	D, 45.6% I, 56.8%	D, 21.5% I, 14.8%	Non-inferiority of a fixed 7-day treatment with D was no achieved FDA warning against D use for VAP.
Wunderink, 2012, ZEPHIR [79]	Linezolid (L) Vancomycin (V)	IV, yes, NI	Meticillin-resistant *Staphylococcus aureus*	HAP + VAP	Clinical outcome at EOS in PP patients	L, 57.6% V, 46.5%	L, 15.7% V, 17%	Nephrotoxicity occurred more frequently with V.
Ramirez, 2013 [80]	Tigecycline low dose (TLD) Tigecycline high dose (THD) Imipenem	II, yes, NI	All pathogens	HAP + VAP	Clinical response at EOT	THD, 85% TLD, 69.6 I, 75%	–	THD could be necessary to treat HAP/VAP.
Awad, 2014 [81]	Ceftobiprole medocaril (C) Ceftazidime + Linezolid (CAZ/L)	III, yes, NI	All pathogens	HAP + VAP	Clinical cure at the TOC	ITT: C, 49.9%; CAZ/L, 52.8% CE: C, 69.3%; CAZ/L, 71.3%	C, 16.7% CAZ/L, 18%	Non-inferiority of C compared with CAZ/L was not demonstrated in VAP patients
Torres, 2018, REPROVE [82]	Ceftazidime/avibactam (CAZ/AVI) Meropenem (M)	III, yes, NI	All pathogens	HAP + VAP	Clinical cure at the TOC	c-mITT: CAZ/AVI, 68.8%; M, 73% CE: CAZ/AVI, 77.4%; M, 78.1%	CAZ/AVI, 8.1% M, 6.8%	CAZ/AVI could be a potential alternative to carbapenems in HAP/VAP patients.
Kollef 2019, ASPECT-NP [83]	Ceftolozane/tazobactam (CFT-TAZ) Meropenem	III, yes, NI	All pathogens	HAP + VAP, only patients on MV	28-day all-cause mortality in ITT	CFT-TAZ, 24% M, 25.3%	CFT-TAZ, 24% M, 25.3%	In HAP and in those in whom previous antibacterial therapy was unsuccessful, CFT-TAZ showed lower mortality.
Cisneros, 2019, Magic-Bullet [84]	Colistin (Co) Meropenen (M)	IV, no, NI	All pathogens	Late VAP	Mortality at 28 days after randomization in mMITT	Co, 23.2% M, 25.3%	Co, 23.2% M, 25.3%	The study was interrupted after the interim analysis due to excessive nephrotoxicity in the colistin group (33.3% vs 18.8%).

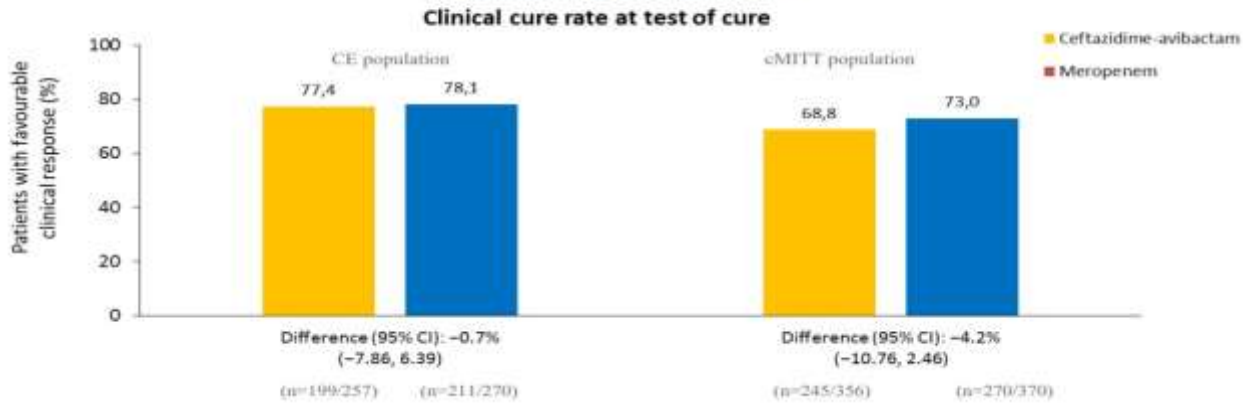
AT all treated patients, *CAZ/AVI* ceftazidime/avibactam, *CE* clinically evaluable population, *CFT-TAZ* ceftolozane/tazobactam, *Co* colistin, *c-mITT* clinical modified intent-to-treat population, *D* doripenem, *EOS* end of study, *EOT* end of treatment, *FU* follow-up, *I* imipenem, *ITT* intention-to-treat population, *M* meropenem, *MITT* modified intent-to-treat population, *mMITT* microbiologically modified intention-to-treat population, *MV* mechanical ventilation, *NI* non-inferiority, *T* tigecycline, *Te* telavancin, *TOC* test of cure, *THD* tigecycline high dose, *TLD* tigecycline low dose, *PP* evaluable per-protocol, *V* vancomycin

Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): a randomised, double-blind, phase 3 non-inferiority trial

Antoni Torres, Nanshan Zhong, Jan Pachl, Jean-François Timsit, Marin Kollef, Zhangjing Chen, Jie Song, Dianna Taylor, Peter J Laud, Gregory G Stone, Joseph W Chow



Ceftazidime-avibactam was non-inferior to meropenem for the treatment of HAP/VAP in this setting



Interpretation Ceftazidime-avibactam was non-inferior to meropenem in the treatment of nosocomial pneumonia. These results support a role for ceftazidime-avibactam as a potential alternative to carbapenems in patients with nosocomial pneumonia (including ventilator-associated pneumonia) caused by Gram-negative pathogens.

Lancet Infect Dis 2018; 18: 285–95

Published Online December 15, 2017 http://dx.doi.org/10.1016/S1473-3099(17)30747-8

See Comment page 229

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Ceftazidime/avibactam in carbapenem- resistant infections

- 36 patients with CRE and 2 with CRPa
  - The most common infections were intra-abdominal and respiratory
- 60.5% life-threatening infections
- The median duration of CAZ-AVI treatment was 16 days
- 65.8% in combination
- 73.7% experienced clinical and/or microbiological cure
- Microbiological cure was associated with improved survival
- CAZ-AVI shows promising clinical results for infections for which treatment options are limited

CRE, carbapenem-resistant *Enterobacteriaceae*; CRPa: carbapenem-resistant *Pseudomonas aeruginosa*

SEFTAZIDIM/ AVIBACTAM[7]

- Termasuk dalam golongan kombinasi sefalosporin/beta laktamase inhibitor
- Aktivitas terhadap *Pseudomonas aeruginosa* dan *Klebsiella pneumonia* resisten Karbapenem yang menghasilkan enzim Karbapenemase tipe KPC dan OXA, tetapi tidak terhadap metalobetalakatamase (MBL).
- Tidak memiliki aktivitas terhadap MDR *Acinetobacter baumanii*
- Indikasi:

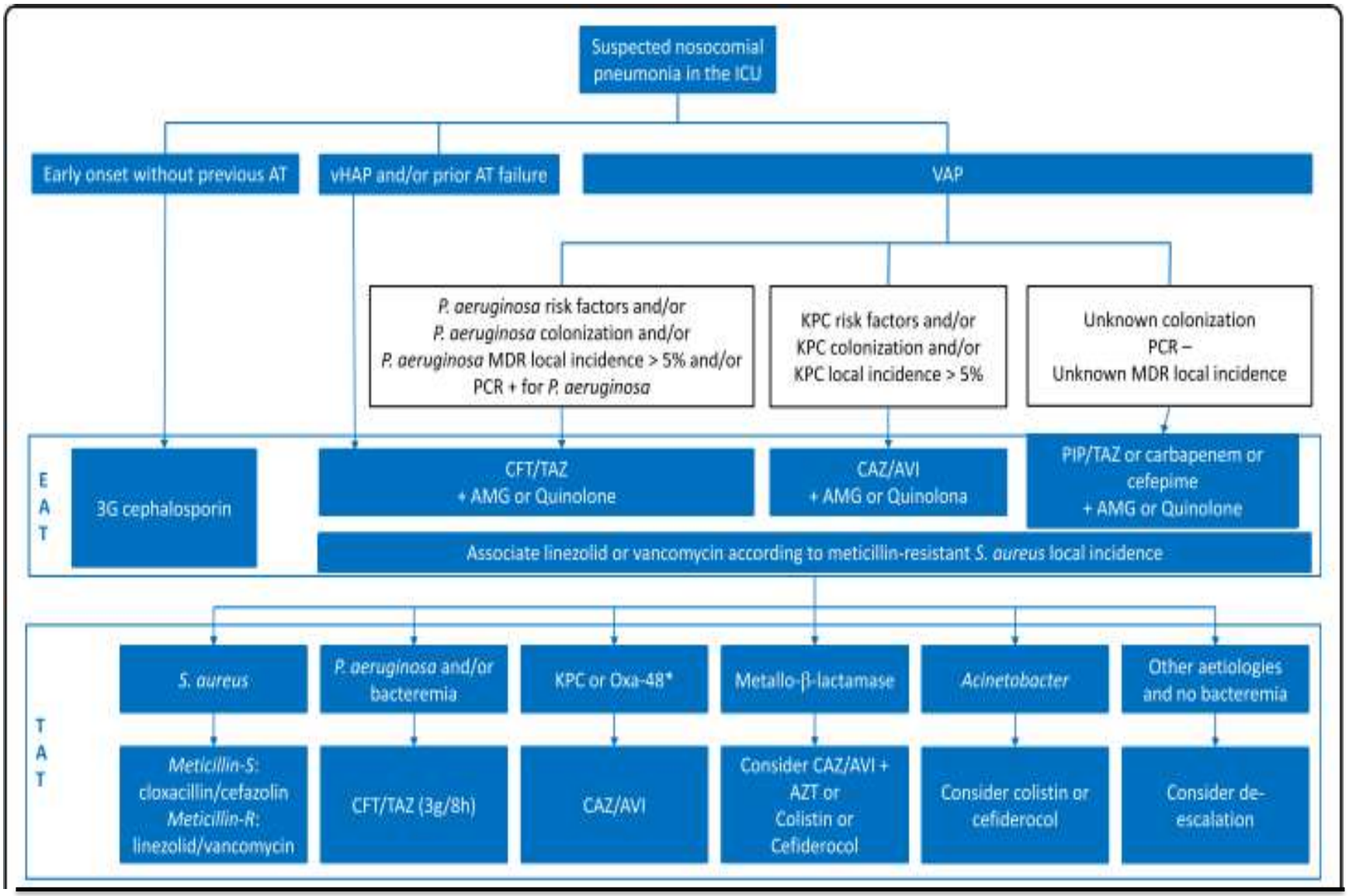
  Definit: infeksi berat/komplikata yang disebabkan XDR Pseudomonas dan *Klebsiella pneumonia* (CRPA dan CRKP) pada saluran kemih (cUTI), intraabdominal (cIAI) , HAP dan VAP

CEFTOLOZANE/TAZOBAKTAM[7]

- Termasuk dalam golongan kombinasi sefalosporin/beta laktamase inhibitor
- Aktivitas terhadap *Pseudomonas aeruginosa* resisten Karbapenem yang menghasilkan Karbapenenmase tipe OXA. Tidak memiliki aktivitas terhadap KPC dan MBL.
- Tidak memiliki aktivitas terhadap *Acinetobacter* dan *carbapenenem-resistant Klebsiella pneumonia.*
- Indikasi:

  Definit: infeksi berat/komplikata yang disebabkan XDR *Pseudomonas aeruginosa* (CRPA) pada saluran kemih (cUTI) dan intra abdominal (cIAI)

Empirical and Targeted Antimicrobial treatment for NP in ICU



Zaragoza *et al. Critical Care* (2020) 24:383
https://doi.org/10.1186/s13054-020-03091-2

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