Treatment of MDR-Pathogens in the Era of Carbapenem Resistant: What are the Evidence?

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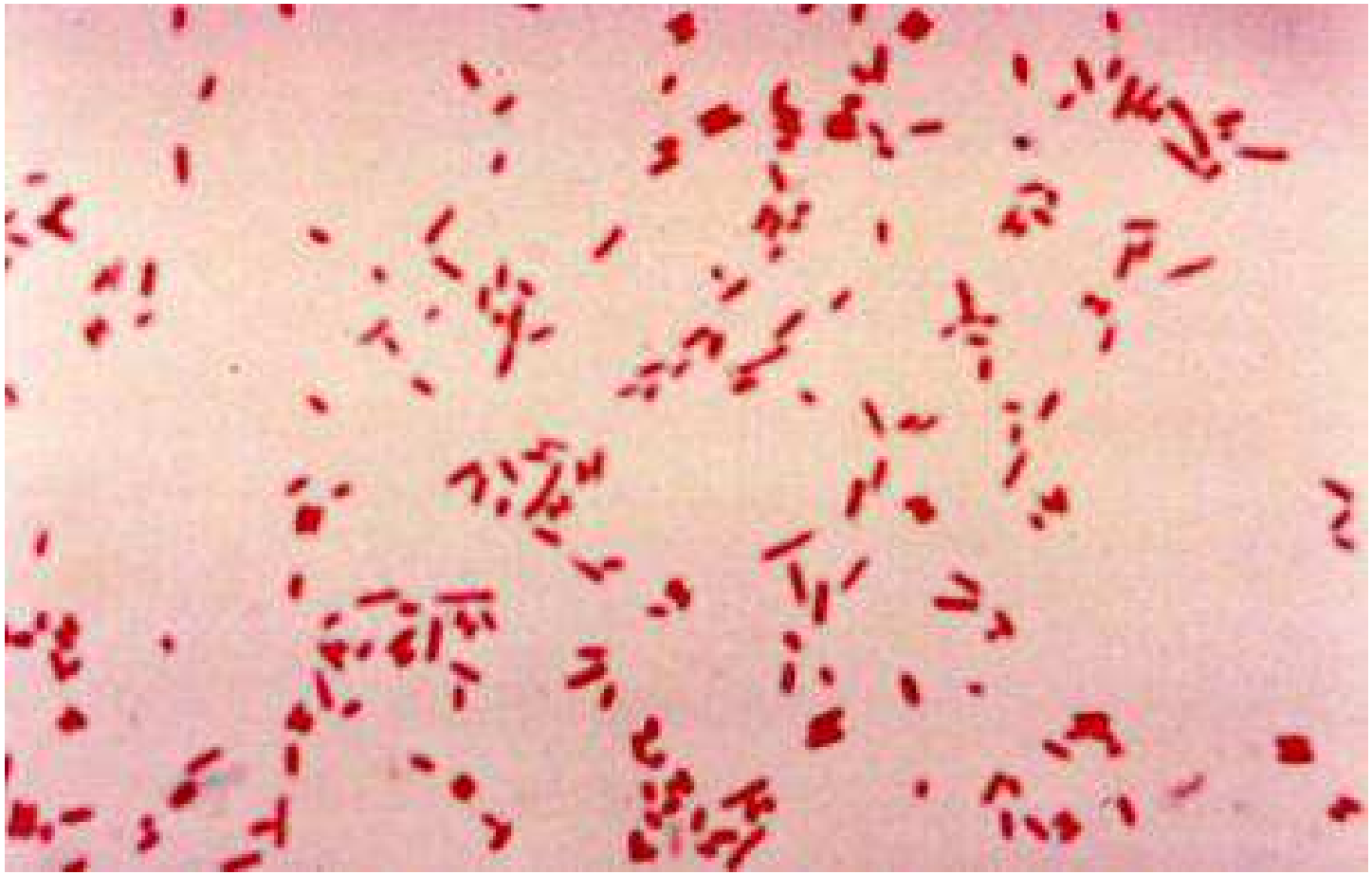
CASE 1

- 55 year-old, with DM type II, cirrhosis admitted to the hospital with fever, chill and lower abdominal tenderness. He had been previously admitted to the hospital last 6 months because of spontaneous bacterial peritonitis treated with CTX and had been seen by physician one month prior to admission.

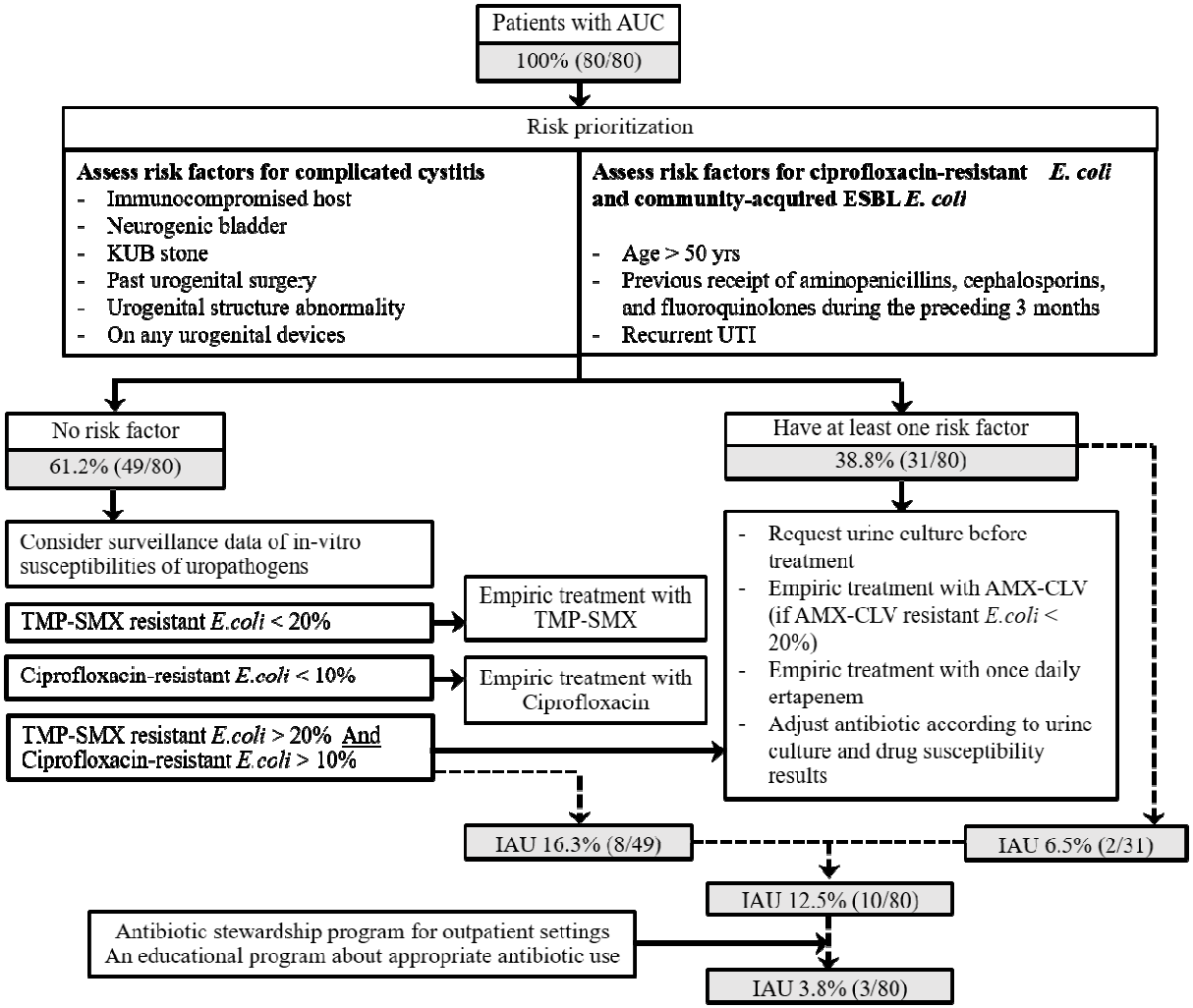
- Upon examination, T 39 C, BP 110./70. RR 24/mins, P 110/min; suprapubic pain was noted and his urinary examination revealed WBC 50 cells/HF with positive nitrite.

Gram stain of blood culture and urine



What is the most appropriate antibiotic at this point?

- A) Ceftriaxone
- B) Quinolone
- C) Carbapenem
- D) Beta-lactam/beta-lactamases
- E) Colistin



Pruetpongpun N, et al. Inappropriate treatment of acute cystitis. Clin Infect Dis 2017

Isolates from blood cultures and urine culture yield ESBL producing *Escherichia coli*

Do carbapenem empirical therapy reduce mortality?

A) Yes B) No C) Not sure

Carbapenems versus alternative antibiotics for the treatment of bacteraemia due to Enterobacteriaceae producing extended-spectrum β-lactamases: a systematic review and meta-analysis

Konstantinos Z. Vardakas[1,2], Giannoula S. Tansarli[1], Petros I. Rafailidis[1,2] and Matthew E. Falagas[1–3]*

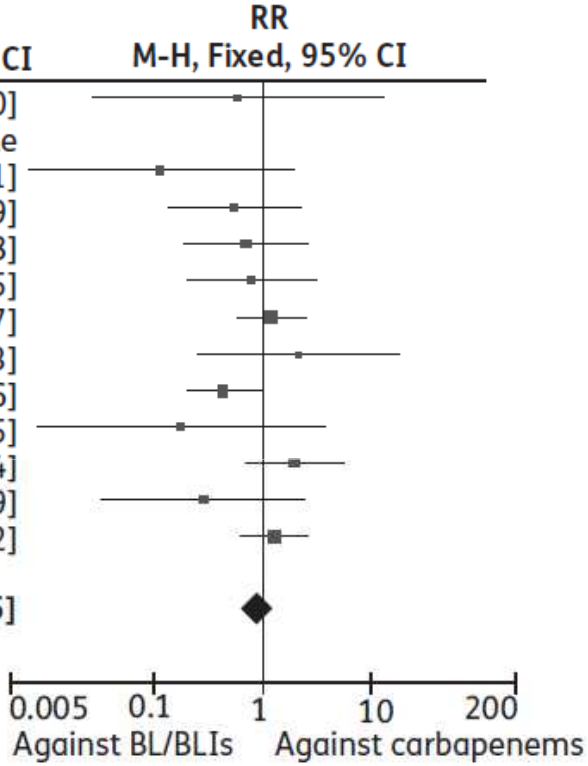
Methods: We searched systematically PubMed and Scopus databases for studies providing data for mortality among patients treated with carbapenems, β-lactam/β-lactamase inhibitor combinations (BL/BLIs) or non-BL/BLIs (mainly cephalosporins and fluoroquinolones), preferably as monotherapy. Studies focusing on patients of all ages with community- and healthcare-associated bacteraemia were eligible. Data were pooled using the technique of meta-analysis.

Results: Twenty-one articles, studying 1584 patients, were included. *Escherichia coli* and *Klebsiella pneumoniae* were the most commonly studied bacteria. Delay in appropriate treatment up to 6 days was reported. Carbapenems were used mainly as definitive therapy. Carbapenems were associated with lower mortality than non- BL/BLIs for definitive [risk ratio (RR) 0.65, 95% CI 0.47–0.91] and empirical (RR 0.50, 95% CI 0.33–0.77) treatment. No statistically significant differences in mortality were found between carbapenems and BL/BLIs administered as definitive (RR 0.52, 95% 0.23–1.13) or empirical (RR 0.91, 95% CI 0.66–1.25) treatment. BL/BLIs were not associated with lower mortality than non-BL/BLIs administered either definitively (RR 1.59, 95% 0.83–3.06) or empirically (RR 0.82, 95% 0.48–1.41). Data regarding subgroups according to the setting, comorbidity and bacterial species could not be extracted.

Study or subgroup	Carbapenems Events	Total	BL/BLIs Events	Total	Weight	RR M-H, Fixed, 95% CI
Apisarnthanarak *et al.* (2008)[19]	0	5	1	10	1.9%	0.61 [0.03, 12.80]
Bin *et al.* (2006)[21]	0	3	0	7		Not estimable
Chaubey *et al.* (2010)[22]	0	10	6	16	9.0%	0.12 [0.01, 1.91]
De Rosa *et al.* (2011)[23]	8	57	2	8	6.2%	0.56 [0.14, 2.19]
Ferrandez *et al.* (2011)[26]	2	6	6	13	6.7%	0.72 [0.20, 2.58]
Gudiol *et al.* (2010)[27]	2	5	3	6	4.8%	0.80 [0.21, 3.05]
Kang *et al.* (2012)[29]	21	78	8	36	19.3%	1.21 [0.59, 2.47]
Lee *et al.* (2010)[30]	4	24	1	13	2.3%	2.17 [0.27, 17.43]
Metan *et al.* (2009)[32]	7	22	5	7	13.4%	0.45 [0.21, 0.96]
Qureshi *et al.* (2011)[34]	0	8	1	4	3.4%	0.19 [0.01, 3.75]
Rodriguez-Bano *et al.* (2012)[14]	6	31	7	72	7.4%	1.99 [0.73, 5.44]
Tumbarello *et al.* (2007)[35]	1	28	4	33	6.5%	0.29 [0.03, 2.49]
Velaphi *et al.* (2009)[20]	13	40	12	48	19.2%	1.30 [0.67, 2.52]
Total (95% CI)		**317**		**273**	**100.0%**	**0.91 [0.66, 1.25]**
Total events	64		56			

Heterogeneity: $\chi^2 = 12.95$; df = 11 ($P = 0.30$); $I^2 = 15\%$

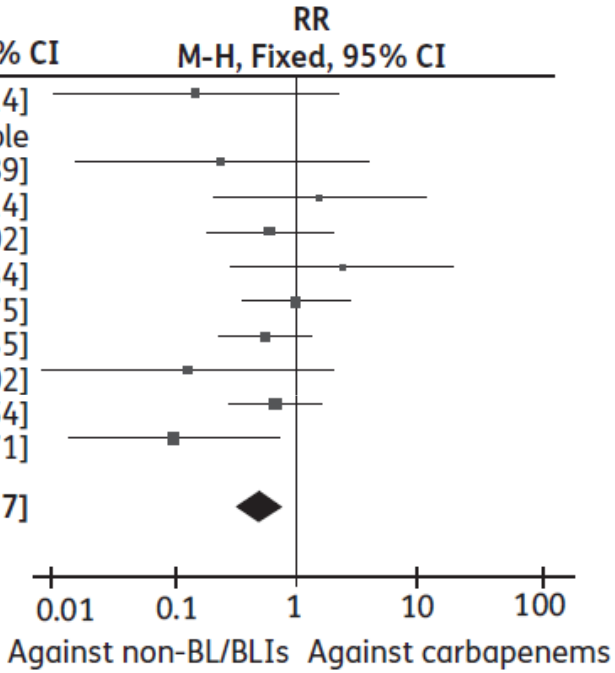
Test for overall effect: $Z = 0.58$ ($P = 0.56$)



Study or subgroup	Carbapenems Events	Total	non-BL/BLIs Events	Total	Weight	RR M-H, Fixed, 95% CI
Apisarnthanarak *et al.* (2008)[19]	0	5	12	21	9.6%	0.15 [0.01, 2.14]
Bin *et al.* (2006)[21]	0	3	0	12		Not estimable
Chaubey *et al.* (2010)[22]	0	10	9	50	6.0%	0.24 [0.02, 3.89]
De Rosa *et al.* (2011)[23]	8	57	1	11	3.0%	1.54 [0.21, 11.14]
Ferrandez *et al.* (2011)[26]	2	6	12	22	9.2%	0.61 [0.19, 2.02]
Gudiol *et al.* (2010)[27]	2	5	1	6	1.6%	2.40 [0.30, 19.34]
Lee *et al.* (2010)[30]	4	24	13	77	11.0%	0.99 [0.36, 2.75]
Metan *et al.* (2009)[32]	7	22	4	7	10.8%	0.56 [0.23, 1.35]
Qureshi *et al.* (2011)[34]	0	8	6	14	8.7%	0.13 [0.01, 2.02]
Rodriguez-Bano *et al.* (2012)[14]	6	31	14	48	19.6%	0.66 [0.29, 1.54]
Tumbarello *et al.* (2007)[35]	1	28	13	36	20.3%	0.10 [0.01, 0.71]
Total (95% CI)		**199**		**304**	**100.0%**	**0.50 [0.33, 0.77]**
Total events	30		85			

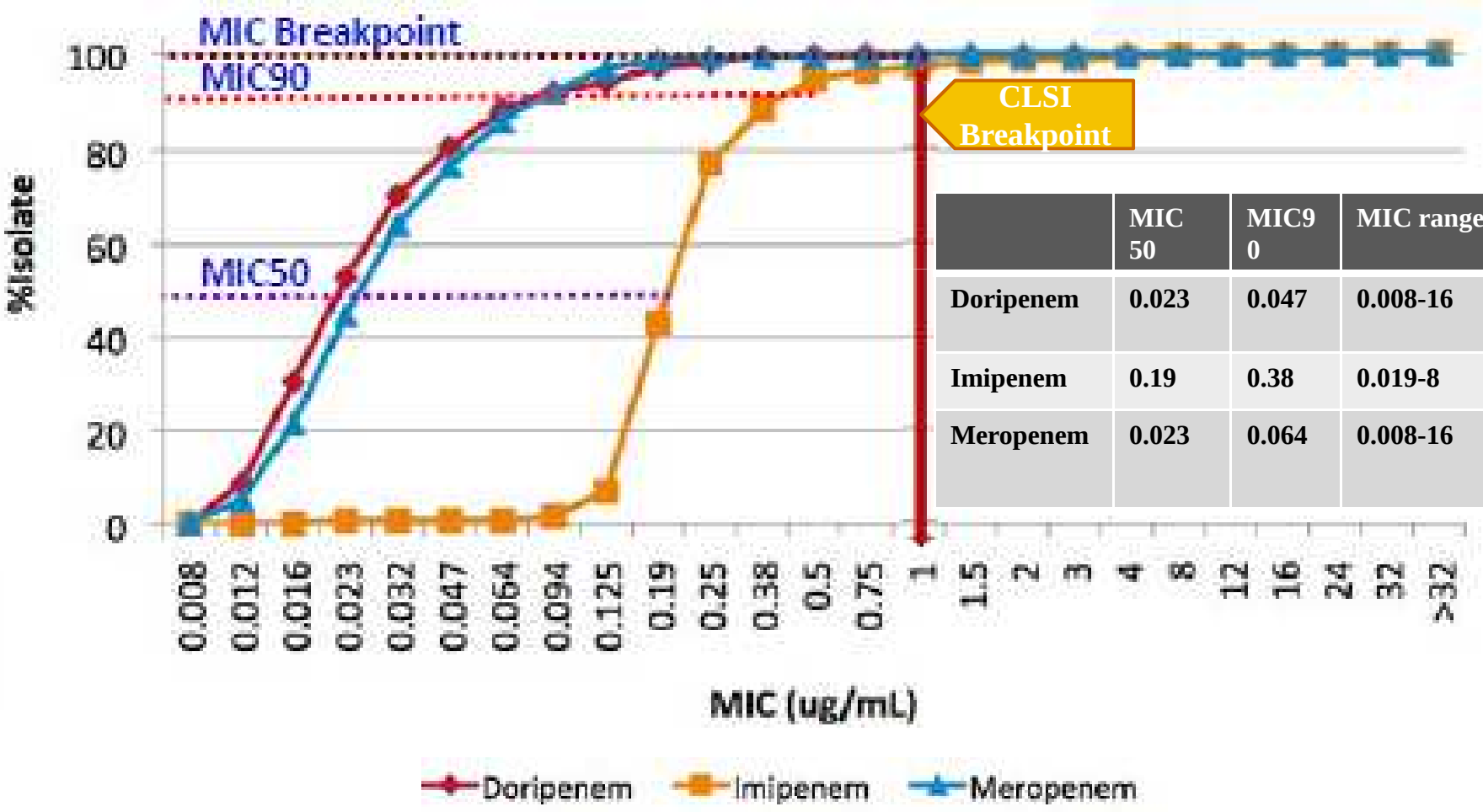
Heterogeneity: $\chi^2 = 10.29$; df = 9 ($P = 0.33$); $I^2 = 13\%$

Test for overall effect: $Z = 3.17$ ($P = 0.002$)



Enterobacteriaceae

500 *Enterobacteriaceae* spp. isolates from ICU and non ICU patients



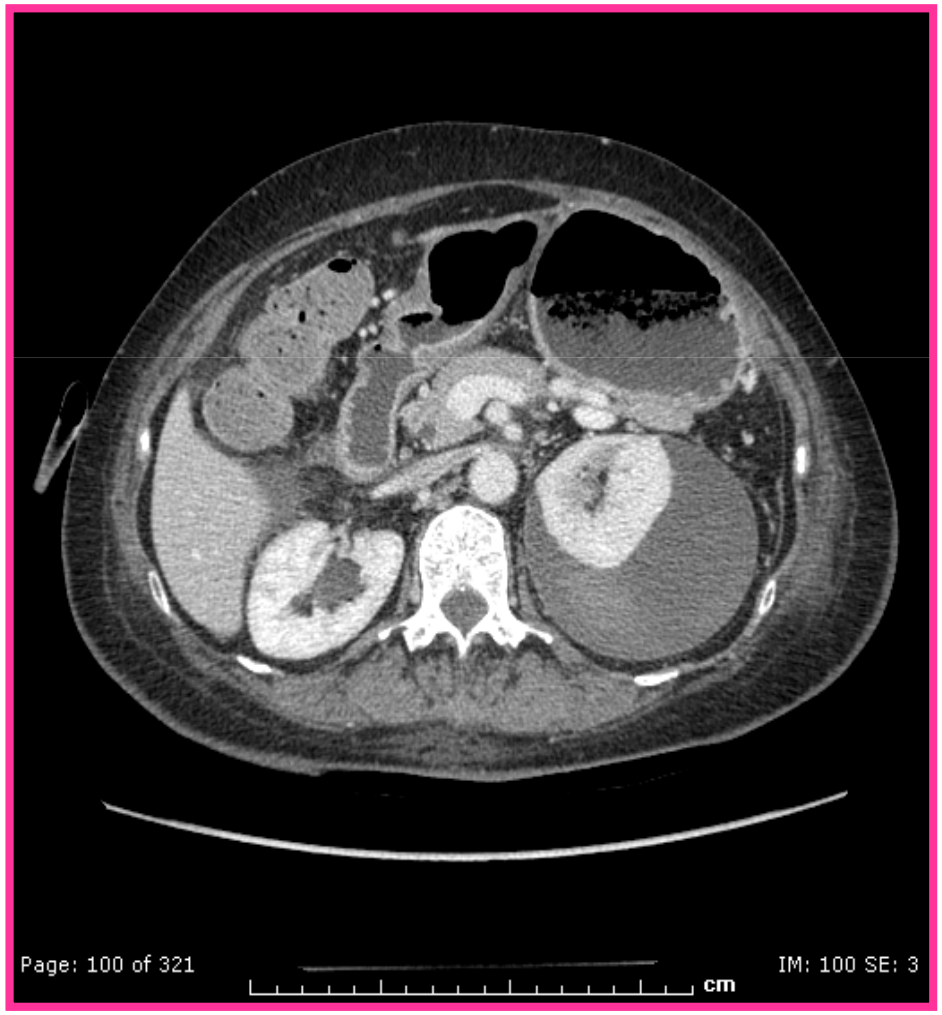
	MIC 50	MIC90	MIC range
Doripenem	**0.023**	**0.047**	**0.008-16**
Imipenem	**0.19**	**0.38**	**0.019-8**
Meropenem	**0.023**	**0.064**	**0.008-16**

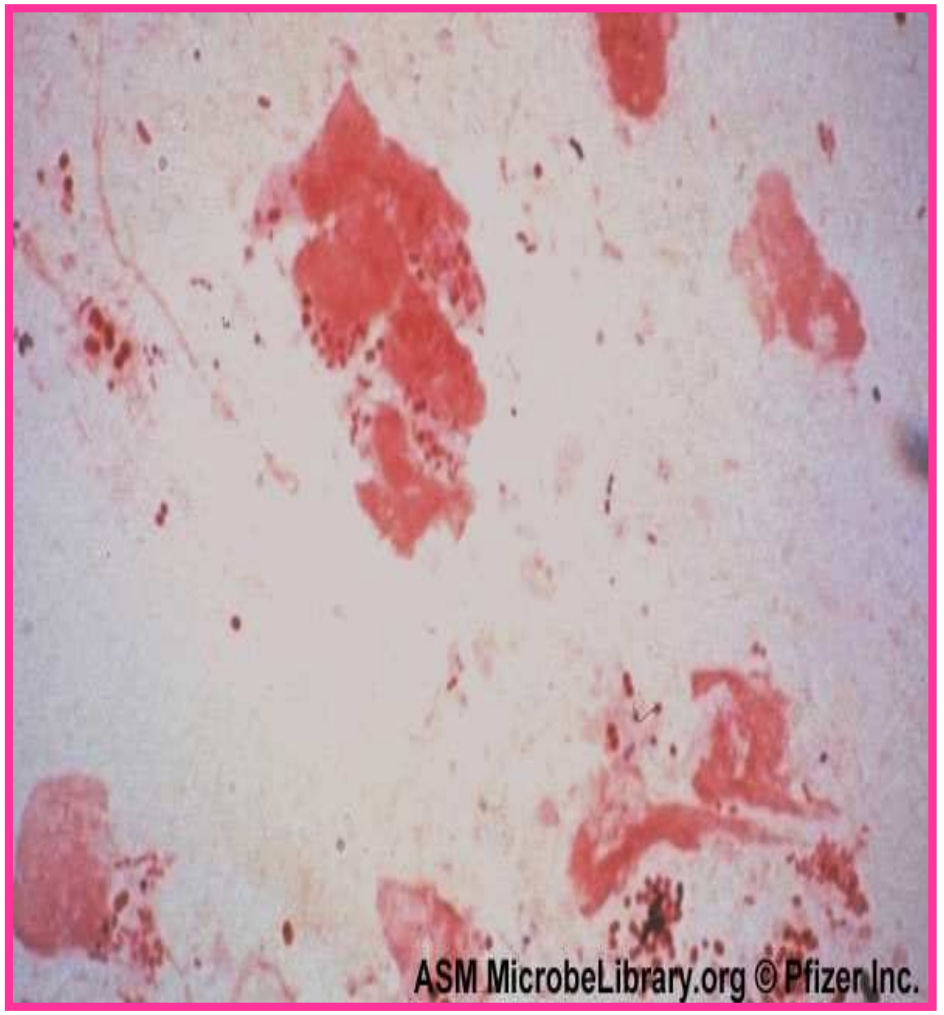
Kiratisin P. et al., COMPACT II, IJAA 39 (2012) 311-316

CASE 2:

- 77 year-old, Thai woman, previously healthy was diagnosed with bladder cancer invaded to colon.
- She underwent radical cystectomy with ileal conduit with intraabdominal drainage.
- There are some outbreak of *XDR-A. baumannii* in this OR during the time of surgery.
- Post-op day 3, abdominal drainage had foul smell and pus was taken for cultures. Culture grew *XDR-A. baumannii*.
- Patient was afebrile, no leucocytosis, but she had marked distended abdomen. Her creatinine = 1.6.
- CT abdomen was performed.

CT abdomen & Gram stain





Resistant Profile for *Acinetobacter baumannii*

Ampicillin	R
Ampicillin/clav	R
Ceftriazone	R
Ceftazidime	R
Cefoperazone/sulbactam	R
Netilmycin	R
Imipenem	R
Meropenem	R
Tigecycline	R
Colistin	S

What is the ATB that you will prescribe?

- A) Colistin
- B) Colistin + a carbapenem
- C) Colistin + Tigeycycline
- D) Colistin + aminoglycoside
- E) I don’t know. Please don’t ask me.

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Carbapenem-Resistant *Acinetobacter baumannii* and *Enterobacteriaceae* in South and Southeast Asia

Li-Yang Hsu,[a,b,c] Anucha Apisarnthanarak,[d] Erum Khan,[e] Nuntra Suwantarat,[f] Abdul Ghafur,[g] Paul Anantharajah Tambyah[b]

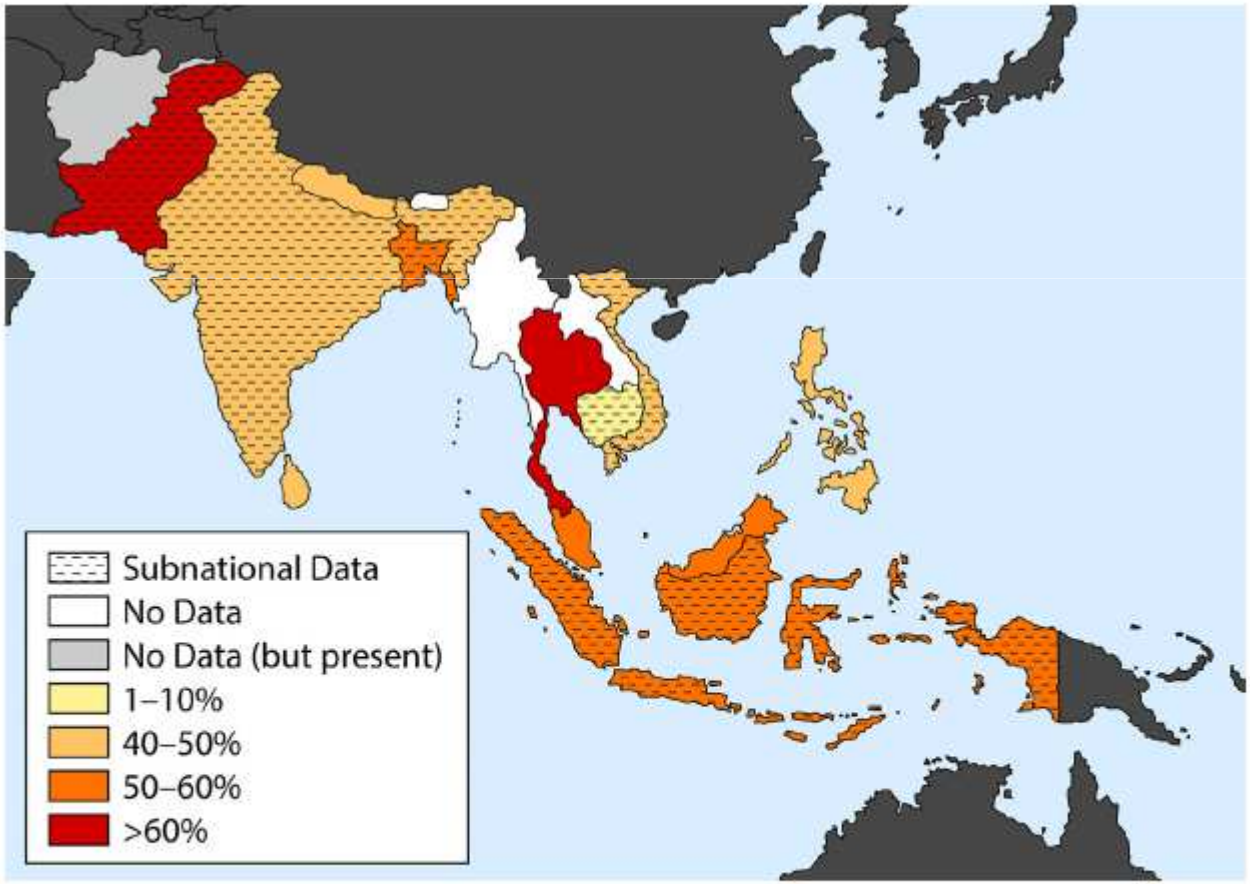
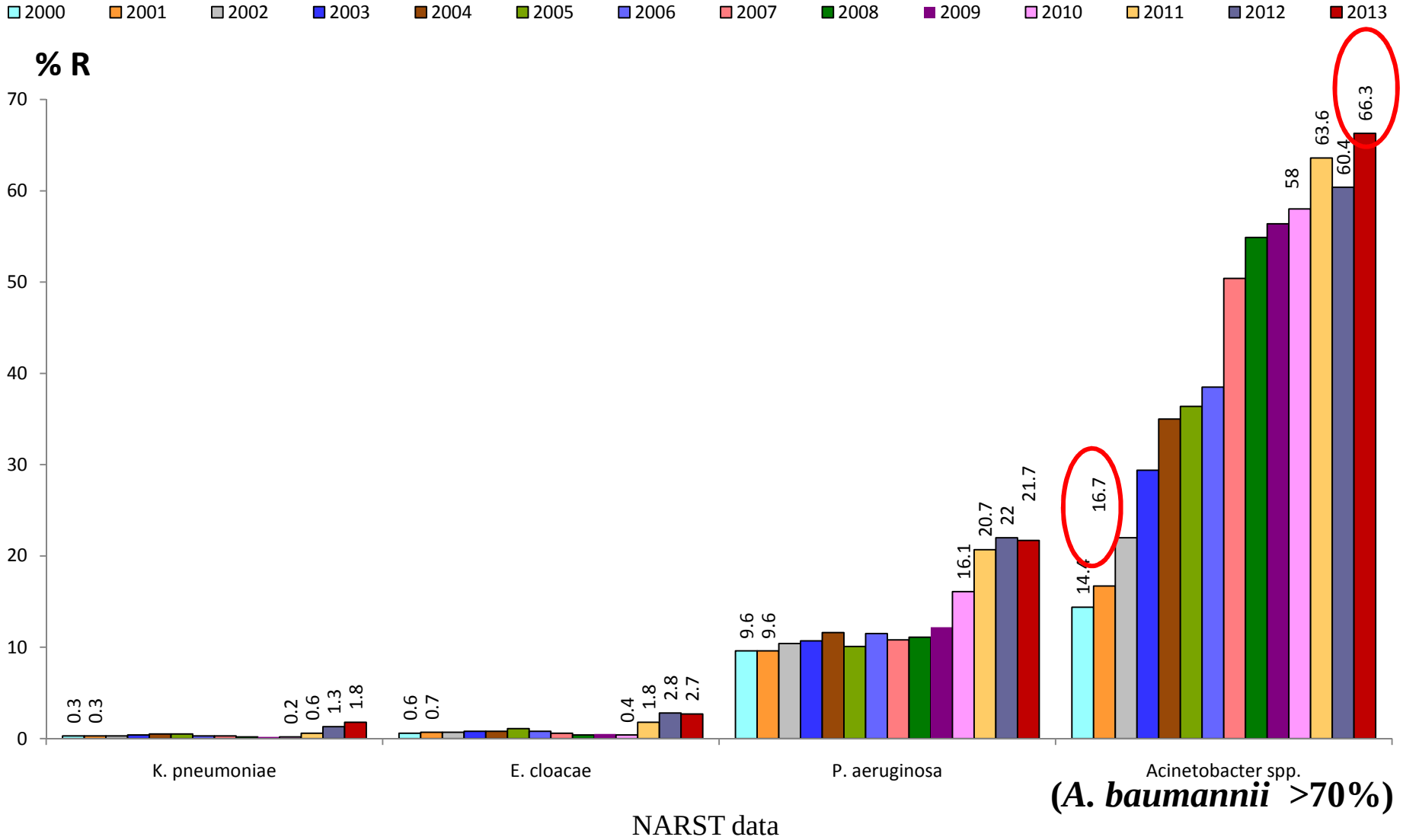


FIG 1 Estimated prevalence of carbapenem-resistant *Acinetobacter baumannii* in South and Southeast Asian countries.

Rate of Imipenem Resistant organisms (28 hospitals, 2000-2013)



(*A. baumannii* >70%)

NARST data

Fatal Outbreak of an Emerging Clone of Extensively Drug-Resistant *Acinetobacter baumannii* With Enhanced Virulence

Crystal L. Jones,[1] Megan Clancy,[2] Cary Honnold,[3] Shweta Singh,[1] Erik Snesrud,[4] Fatma Onmus-Leone,[4] Patrick McGann,[4] Ana C. Ong,[4] Yoon Kwak,[4] Paige Waterman,[4] Daniel V. Zurawski,[1] Robert J. Clifford,[4] and Emil Lesho[4]

[1]Department of Wound Infections, Walter Reed Army Institute of Research, Silver Spring, Maryland; [2]Providence Alaska Medical Center, Anchorage; [3]Department of Pathology, and [4]Multidrug-Resistant Organism Repository and Surveillance Network, Walter Reed Army Institute of Research, Silver Spring, Maryland

(See the Editorial Commentary by Paterson and Harris on pages 155–6.)

Background. Severe *Acinetobacter baumannii* infections in immunocompetent patients are uncommon, and the virulence mechanisms of this organism are not fully understood.

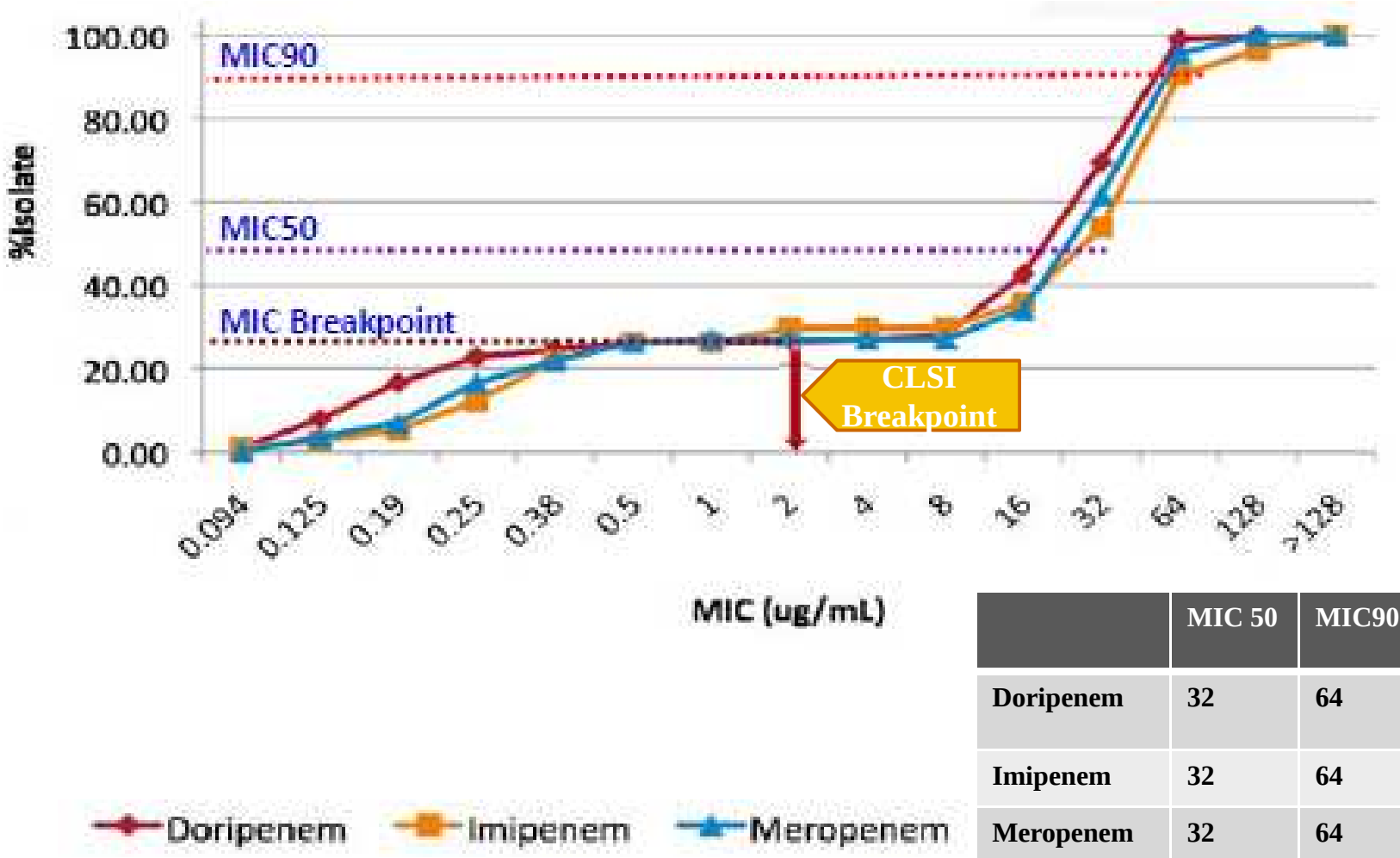
Methods. Following an outbreak of fatal *A. baumannii* infections in a cohort of relatively immunocompetent patients (low comorbidity and illness severity scores), isolates were investigated with comparative genomics and in animal models.

Results. Two unrelated *A. baumannii* clades were associated with the outbreak. The clone associated with the majority of patient deaths, clade B, is evolutionarily distinct from the 3 international clonal complexes, belongs to multilocus sequence type (MLST) 10, and is most closely related to strains isolated from the Czech Republic, California, and Germany in 1994, 1997, and 2003, respectively. In 2 different murine models, clade B isolates were more virulent than comparator strains, including the highly virulent reference strain AB5075. The most virulent clade B derivative, MRSN 16897, was isolated from the patient with the lowest combined comorbidity/illness severity score. Clade B isolates possess a unique combination of putative virulence genes involved in iron metabolism, protein secretion, and glycosylation, which was leveraged to develop a rapid and specific clinical assay to detect this clade that cannot be distinguished by MLST.

Conclusions. Clade B warrants continued surveillance and investigation.

Acinetobacter baumannii

115 *Acinetobacter baumannii* isolates from ICU and non-ICU patients



	MIC 50	MIC90	MIC range
Doripenem	**32**	**64**	**0.125-128**
Imipenem	**32**	**64**	**0.094->128**
Meropenem	**32**	**64**	**0.125-128**

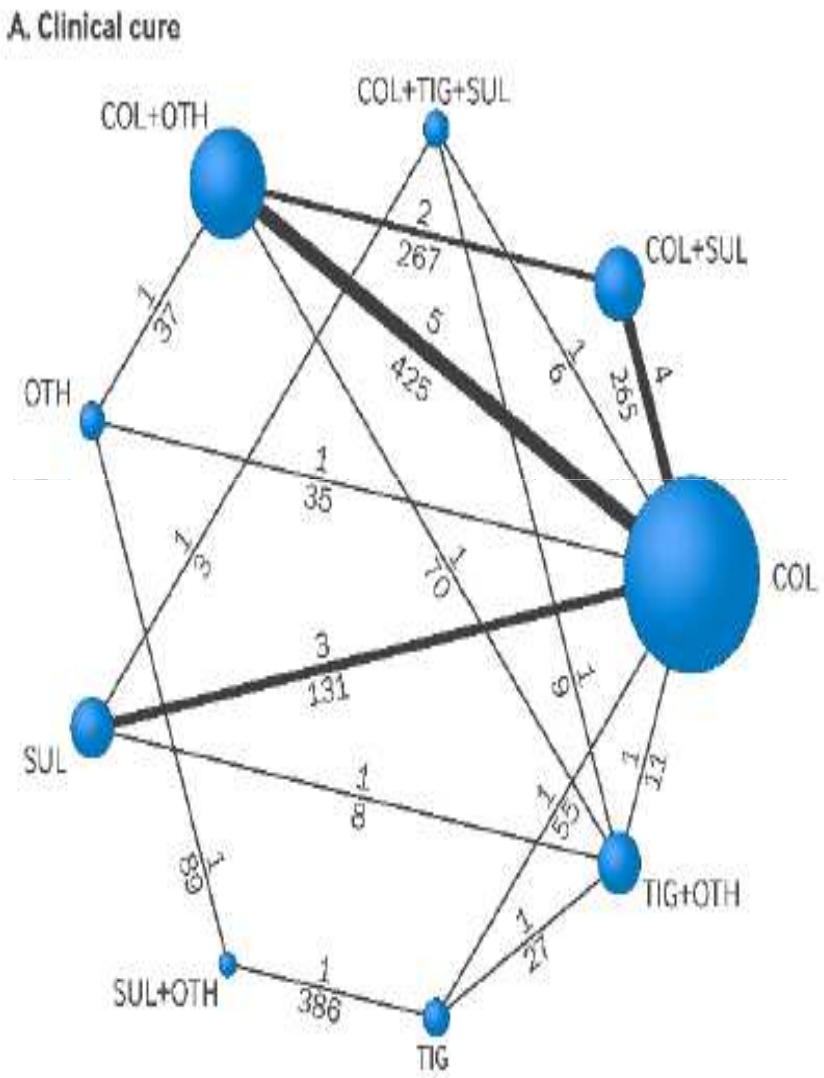
Kiratisin P. et al., COMPACT II, IJAA 39 (2012) 311-316

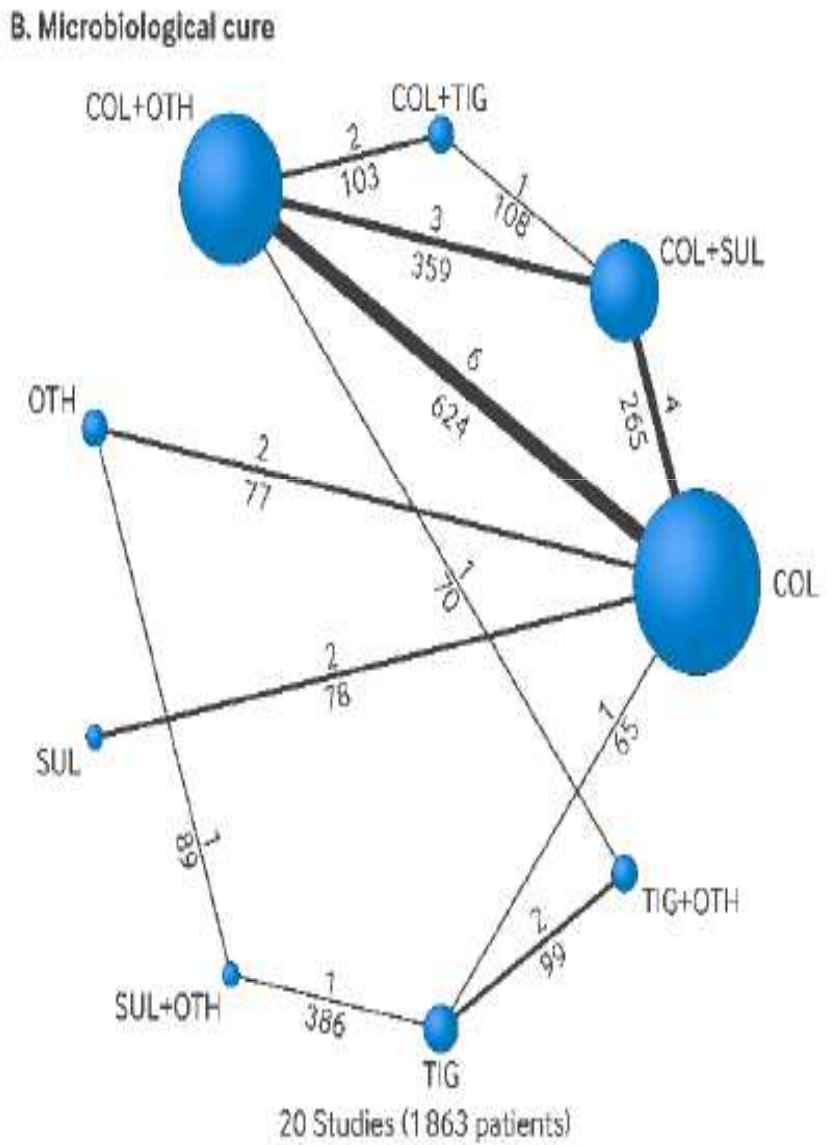
Comparative efficacy and safety of treatment options for multidrug-resistant and extensively drug-resistant Acinetobacter baumannii (MDR and XDR-AB) infections: a systematic review and network meta-analysis.

Kirati Kengkla[1], Khachen Kongpakwattana[2], Surasak Saokaew[1,2,5], Anucha Apisarnthanarak[3], Nathorn Chaiyakunapruk[2,5,7].

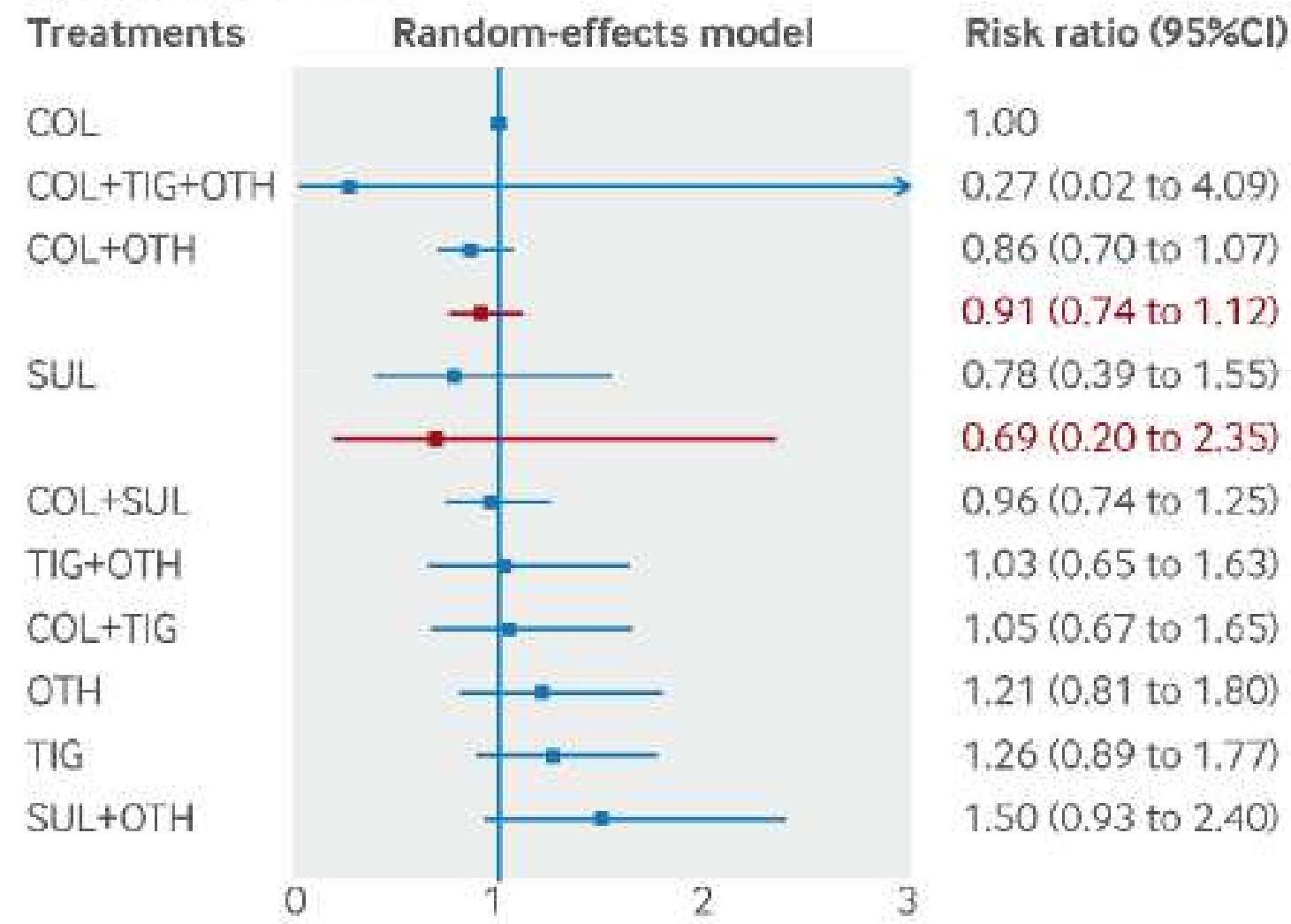
Methods We did a systematic review and network meta-analysis (NMA). We searched PubMed, Embase and the Cochrane register of trials for Randomised controlled trials (RCTs) or observational studies that examined treatment options (colistin, sulbactam, tigecycline, or other antibiotics as monotherapy, combination or triple therapy) in patients with MDR- and XDR-AB infections from inception to April 18, 2016. Primary outcomes were clinical cure and microbiological cure. Secondary outcomes were all-cause mortality, nephrotoxic and non-nephrotoxic adverse events. We performed NMA to estimate risk ratios with 95% confidence intervals using RCTs alone and RCTs with observational studies.

Findings 4 RCTs and 25 observational studies with 2529 patients (median age, 60 years; 65% male; median APACHE II, 19.0) were included. In NMA, when compared with colistin monotherapy, colistin combination therapy was significantly associated with improving microbiological cure (RR 1.21; 95%CI, 1.10 to 1.42). The nephrotoxic events of colistin-based combination therapy were similar to those of colistin monotherapy. No significant differences in clinical cure as well as all-cause mortality were noted among treatment options.


A. Clinical cure
COL+OTH
COL+TIG+SUL
COL+SUL
OTH
COL
SUL
TIG+OTH
SUL+OTH
TIG
17 Studies (1 476 patients)


B. Microbiological cure
COL+OTH
COL+TIG
COL+SUL
OTH
COL
SUL
TIG+OTH
SUL+OTH
TIG
20 Studies (1 863 patients)

C. All-cause mortality



Take Home Messages

- No regimen provide better clinical outcomes compared to COL monotherapy, although combination regimen provide better microbiological outcomes (may be helpful in infection control aspect).

- Further investigations on triple therapy should provide some insights into the treatment of *XDR-Acinetobacter baumannii*

Case 3

- 65 year-old, patient with COPD, mild renal insufficiency (cr = 1.7) was admitted for COPD exacerbation. His admission was complicated by hospital acquire pneumonia on hospital day 7.

- Sputum culture grew: Carbapenem-Resistant *Pseudomonas aeruginosa*

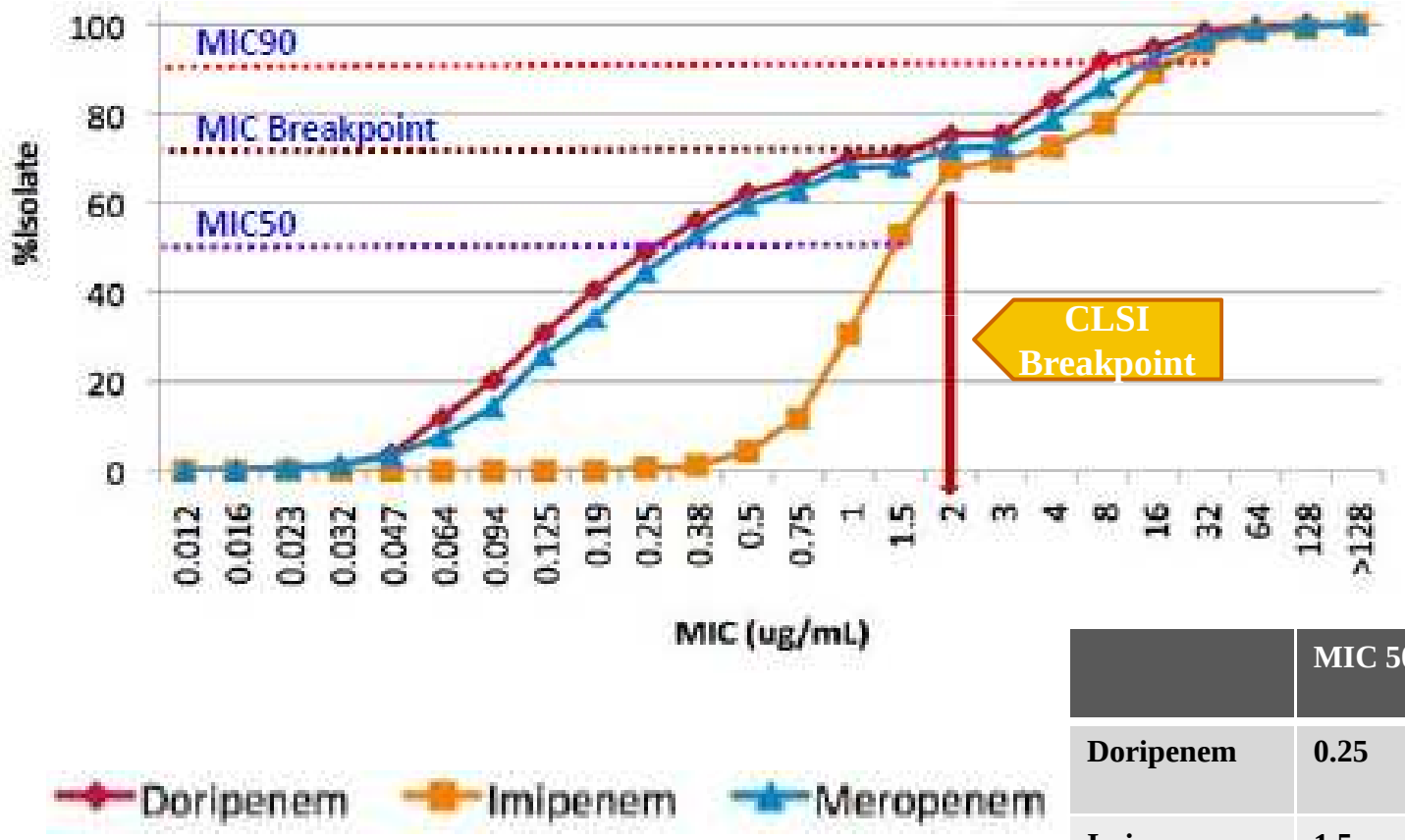
- R to Imipenem, Meropenem and I to Doripenem

What will you do next?

- A) Start colistin monotherapy
- B) Start colistin combination therapy
- C) Use Doripenem (1g in 4 hrs q8h) + colistin, if MIC dori <16
- D) Use Doripenem (1g in 4 hrs q8h) + fosfomycin, if MIC dori <16

Pseudomonas aeruginosa

***625 Pseudomonas aeroginosa* isolates from ICU and non-ICU patients**



	MIC 50	MIC90	MIC range
Doripenem	**0.25**	**8**	**0.032-128**
Imipenem	**1.5**	**16**	**0.38-128**
Meropenem	**0.38**	**16**	**0.032->128**

Kiratisin P. et al., COMPACT II, IJAA 39 (2012) 311-316

Microbiology and Immunology

Microbiol Immunol 2013; 57: 170–178
doi: 10.1111/1348-0421.12021

ORIGINAL ARTICLE

Molecular investigation of carbapenem resistance among multidrug-resistant *Pseudomonas aeruginosa* isolated clinically in Thailand

Piyatip Khuntayaporn[1], Preecha Montakantikul[2], Pitak Santanirand[3], Pattarachai Kiratisin[4] and Mullika Traidej Chomnawang[1]

ABSTRACT

Carbapenem resistant *Pseudomonas aeruginosa* were isolated among multidrug-resistant (CR-MDR) organisms from tertiary hospitals in Thailand. Decreased expression of *oprD* mRNA (93.65%) was predominant followed by increased expression of *mexAB-oprM* mRNA (92.06%) and *mexXY* mRNA (63.49%). Interestingly, 23 of 126 (18.25%) isolates were susceptible to imipenem with down-regulated *oprD* expression and non-up-regulated *mexCD-oprJ* mRNA expression. Metallo-β-lactamases production was clearly positive in 24 isolates (18.46%) and weakly positive in 12 isolates (9.23%). Among both of these sets of isolates, *imp-1*, *imp-14* and *vim-2* were identified. Hyperproduction of AmpC β-lactamase had the lowest prevalence rate (3.97%). It was concluded that CR-MDR *P. aeruginosa* clinical isolates in Thailand possess multifactorial resistance mechanisms.

Synergistic effects of fosfomycin and carbapenems against carbapenem-resistant *Pseudomonas aeruginosa* clinical isolates

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Mullika Traidej Chomnawang*

Treatment of *P. aeruginosa* with doripenem alone resulted in cell disruption and abnormal bacterial cell shape as determined by scanning electron microscopy. Treatment with fosfomycin alone showed less activity in bacterial cell destruction. When fosfomycin was combined with doripenem at 0.25× MIC, extreme disruption of the bacterial cell membrane and morphological changes occurred. This effect was obviously stronger than following treatment with a single antibiotic. In conclusion, the combination of fosfomycin plus a carbapenem could be of interest as an alternative therapeutic for

This study demonstrated that doripenem showed promising activity when combined with fosfomycin (45.7% synergy), followed by meropenem (40.0%) and imipenem (38.6%). Considering all

Optimizing intravenous fosfomycin dosing in combination with carbapenems for treatment of *Pseudomonas aeruginosa* infections in critically ill patients based on pharmacokinetic/pharmacodynamic (PK/PD) simulation

O. Asuphon [a], P. Montakantikul [b], J. Houngsaitong [b], P. Kiratisin [c], P. Sonthisombat [a,*]

A B S T R A C T

Objective: The purpose of the study was to determine the optimal dosing regimen of intravenous fosfomycin for the treatment of *Pseudomonas aeruginosa* (PA) based on PK/PD targets.

Method: A total of 120 PA isolates were recovered from various clinical specimens at university hospital in Thailand. Minimum Inhibitory Concentrations (MICs) of all the isolates were determined by the E-test method. PK parameters were obtained from a published study. Monte Carlo simulation was performed to calculate the percentage of target attainment (PTA) and cumulative fraction of response (CFR).

Results: MIC_{90} of fosfomycin alone, fosfomycin in combination with carbapenem, carbapenems alone and carbapenems in combination with fosfomycin were >1,024, 1,024, >32 and 32 μg/ml, for multidrug resistant (MDR)-PA and 512, 128, 8 and 3 μg/ml respectively, for non-MDR PA. Approximately 40% of the non-MDR PA were carbapenem-resistant strains. For non-MDR PA with CRPA, fosfomycin 16 g continuous infusion in combination with carbapenems provided %PTA of approximately 80 and %CFR of > 88. While, %PTA and %CFR > 90 were achieved with fosfomycin 24 g/day prolonged infusion in combination with carbapenem.

Conclusions: Prolonged infusion of fosfomycin 16 - 24 g combined with extended carbapenem infusion could be used in non-MDR PA treatment with CRPA.

Table 1

MICs of non-MDR PA and MDR PA isolates against tested agents, mono drugs and combination drugs.

Antimicrobial agent	Antimicrobial mono and combination drugs	Non-MDR			MDR#	
		MIC range (μg/ml)	MIC_{90} (μg/ml)	MIC_{90} Of CRPA* (μg/ml)	MIC range (μg/ml)	MIC_{90} (μg/ml)
Imipenem	monodrug	0.75 - >32	>32	>32	1.0->32	>32
	IPM + FOF	0.047 - > 32	12	12	0.38-32	32
Meropenem	monodrug	0.016 - >32	8	>32	1.0->32	>32
	MEM + FOF	0.006 - 32	3	6	0.38-32	32
Doripenem	monodrug	0.023 - >32	4	6	0.5->32	>32
	DOM + FOF	0.006 - >48	2	2	0.38-32	32
Fosfomycin	monodrug	1.5 - >1024	512	>1024	8.0 - >1024	>1024
	FOF + IPM	1.0 - 1024	128	192	8.0 - 1024	1024
	FOF + MEM	0.75 - 1024	128	192	8.0 - 1024	1024
	FOF + DOM	0.064 -1024	128	128	8.0 - 1024	1024

Table 2

The maximum of %PTA for fosfomycin (FOF) achive more than 70% time above MIC_{90} and carbapenem (doripenem (DOM), imipenem (IPM), meropenem (MEM)) 40% time above MIC_{90} of non MDR-PA* when combinations.

%PTA of combinations	IPM 1 g q 8 h	IPM 1 g in 3 h q 8 h	DOM 1 g q 8 h	DOM 1 g in 4 h q 8 h	MEM 1 g q 8 h	MEM 1 g in 3 h q 8 h	MEM 2 g q 8 h	MEM 2 g in 3 h q 8 h
FOF 4 g q 12 h	0	0	0	0	0	0	0	0
FOF 8 g q 12 h	0	0	0	0	0	0	0	0
FOF 4 g q 8 h	1	2	2	3	3	3	3	3
FOF 4 g q 6 h	11	23	23	24	24	24	24	24
FOF 8 g q 8 h	30	30	49	49	49	49	50	50
FOF 16 g continuous infusion	32	33	77	80	80	80	80	80
FOF 8 g in 6 h q 8 h	34	35	93	95	95	96	96	96

Use of Doripenem with fosfomycin for Carbapenem resistant *P. aeruginosa*

Patient	Sex	Age, years	Comorbid condition(s)	Empiric antibiotic regimen	Time to receipt of combination regimen, days	Clinical outcome	Microbiological outcome
1	M	56	DM, HTM	Mer, SPZ, Net	1	Cure	Eradication
2	M	61	HTN, COPD	Imi, Gen	1	Cure	Eradication
3	M	67	DM, cirrhosis, COPD	SPZ, Mer, Net	1	Cure	Eradication
4	M	71	HTN, cirrhosis	Mer, Gen	1	Cure	Eradication
5	M	73	Neurological disorder	Imi, Net	2	Cure	Eradication
6	F	47	DM, HTN	Mer, SPZ, Net	1	Cure	Eradication
7	F	39	Cirrhosis	Imi, Gen	1	Failure (death)	Eradication
8	F	61	DM	Pip-Taz, Mer	2	Failure (death)	Persistence

Apisarnthanarak A, et al. Use of doripenem with fosfomycin for treatment of carbapenem resistant *Pseudomonas aeruginosa*. Clin Infect Dis 2011

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ksantiwi, 3/17/2011

Carbapenem-resistant *Pseudomonas aeruginosa* pneumonia with intermediate minimum inhibitory concentrations to doripenem: combination therapy with high-dose, 4-h infusion of doripenem plus fosfomycin (16 g/d) versus intravenous colistin plus fosfomycin (16 g/d)

Characteristic	Doripenem/fosfomycin[a] (N = 25)	Colistin/fosfomycin[b] (N = 24)	P-value
Age (years) (median)	45 46 0.79	46	0.79
Sex (female) [n (%)]	10 (40)	11 (46)	0.69
Underlying diseases [n (%)]			
Diabetes	5 (20)	4 (17)	0.79
Hypertension	4 (16)	4 (17)	
COPD	6(24)	8(33)	
Cirrhosis	5(20)	5(21)	
Neurological diseases	5 (20)	6 (25)	
Type of nosocomial pneumonia [n (%)]			
VABP	15 (60)	14 (58)	0.93
HABP	10 (40)	10 (42)	
Receipt of empirical antibiotic [n (%)]	25(100)	24(100)	N/A
Time to receipt of combination therapy (days) [median (range)][c]	1 (1–2)	1 (1–2)	0.89

Apisarnthanarak A & Mundy LM. Int J Antimicrob Agent, 39 (2012) 271-272

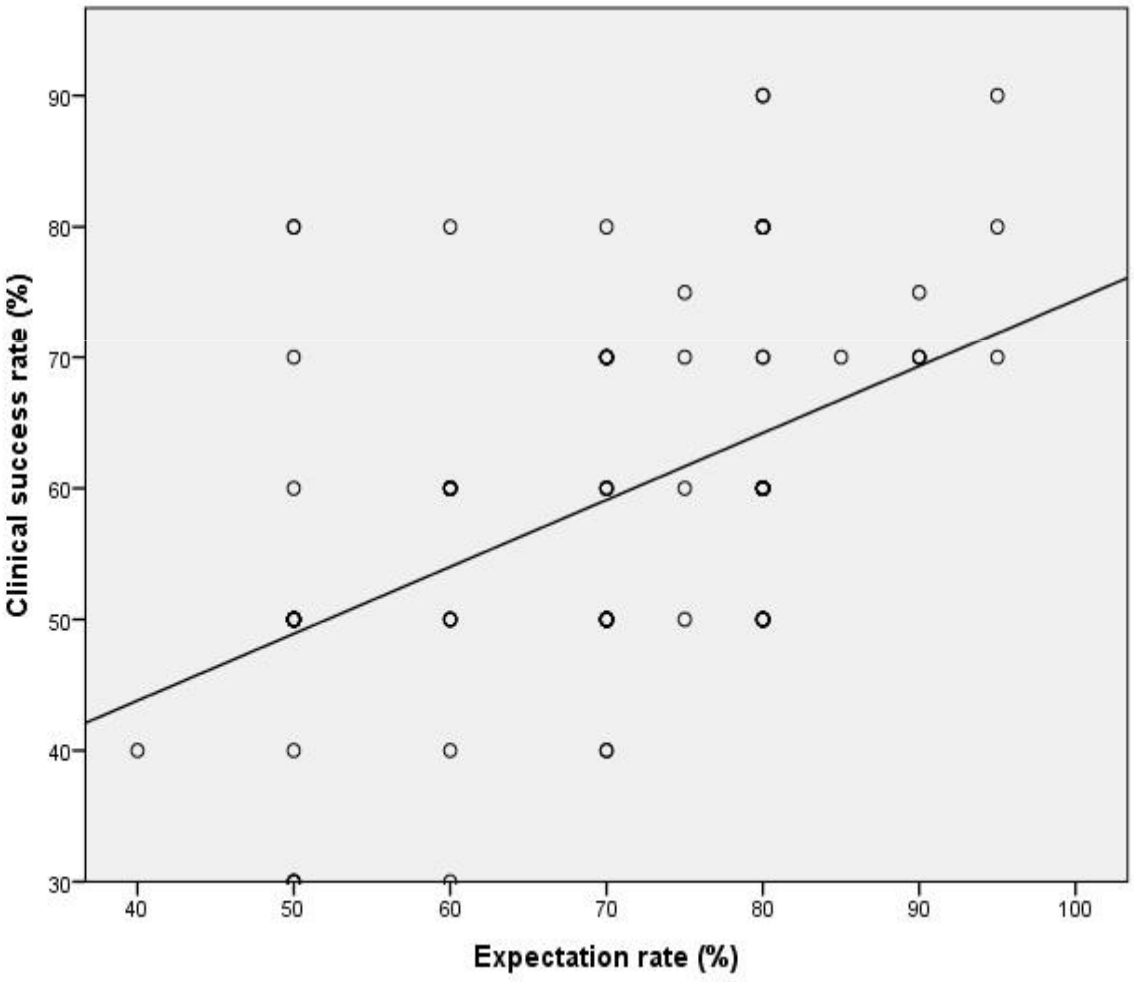
Outcomes

Characteristic	Doripenem/fosfomycin[a] (N = 25)	Colistin/fosfomycin[b] (N = 24)	P-value
Outcomes [n (%)]			
Clinical cure	**15 (60)**	**14 (58)**	0.91
Microbiological cure	18(72)	15(63)	0.48
All-cause (28-day) mortality [n (%)]	10 (40)	10 (42)	0.9
Any serious adverse drug events [n (%)][d]	**0 (0)**	**2 (8)**	0.24

COPD, chronic obstructive pulmonary disease; VABP, ventilator-associated bacterial pneumonia; HABP, hospital-acquired bacterial pneumonia.
a One gram, 4-h infusion of doripenem in combination with fosfomycin for ≥2 days.
b Intravenous colistin (5 mg/kg/day in two divided doses) in combination with fosfomycin for ≥2 days.
c Time from report of P. aeruginosa susceptibility to receipt of combination regimen.
d Renal failure (defined as an increase in creatinine of >1.5× baseline creatinine), any neurological abnormality (e.g. paralysis, seizure) or drug rash; both patients in the
colistin + fosfomycin group had evidence of reduced creatinine clearance of 25% of baseline creatinine clearance.

Apisarnthanarak A & Mundy LM. Int J Antimicrob Agent, 39 (2012) 271-272

Increasing Awareness on Infection Control among IDP were associated with better treatment outcome for VAP due to XDR-Acinetobacter



"Working in hospital that implement standard together with intensified IC for CRAB (*P*=0.02) was associated with high expected rate (>60%), while being board certified IDPs (*P*<0.01) and having higher number of ID consultation cases/month (*P*<0.01) were associated with high clinical success rate (>60%)."

Buppajarntham A, et al. National survey of Thai IDP on treatment of XDR-AB VAP. ICHE 2016

Conclusions

- MDR-pathogens will continue to emerge while antibiotic is limited.
- Treatment of MDR-pathogens will remain a challenges in the years to come.
- Successful treatment outcomes require several strategies (e.g., PK/PD, combination therapy, and awareness in infection control)


Thank you very much for your attention

Monte Carlo Simulation 10,000 Subjects COMPACT Study