MULTIRESISTANT GRAM-NEGATIVE BACTERIA: INTERVENTIONAL STRATEGIES, CURRENT CLINICAL EXPERIENCE

Dr Le Thi Thuy Dung
Neonatal Deparment.

Multidrug-resistant enterobacteriae

- The first reports of carbapenemases (hydrolyzing b-lactamases) were reported in the early 1990s .

- Enterobacteriaceae that produce K. pneumoniae carbapenemases (KPCs) have subsequently spread worldwide, where they are associated with serious, nosocomial, systemic infections.

- There remain limited therapeutic options to treat infections caused by carbapenem-resistant enterobacteria.

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Carbapenemases

- Organized based on amino acid homology in the Ambler molecular classification system.
- Class A, C, and D beta-lactamases all share a serine residue in the active site.
- Class B enzymes require the presence of zinc for activity.
- Classes A, B, and D are of greatest clinical importance among nosocomial pathogens

Clin Microbiol Infect 2011; 17: 1135–1141

Klebsiella pneumoniae carbapenemase (KPC)

- The most clinically important of the Class A carbapenemases.
- Reside on transmissible plasmids and confer resistance to all beta-lactams (E. coli, Pseudomonas aeruginosa, Enterobacter spp,ect.)

UpToDate, Aug 22, 2012

Organism	MBLs (class B)	Class A KPC (GES)	OXA (class D)
Pseudomonads			
Pseudomonas aeruginosa	++	+	+
Pseudomonas putida	+	+	
Acinetobacter baumannii	+[a]		++
Acinetobacter spp.	+		+
Enterobacteria			
Klebsiella pneumoniae	+[a]	++	+
Escherichia coli	+	+	+
Proteus mirabilis	+		+
Providencia spp.	+		
Klebsiella oxytoca	+	+	
Serratia marcescens	+[a]	+	
Enterobacter spp.	+[a]	+	

Minimum Inhibitory Concentration (MIC)

- Necessary to choose optimal therapy for infection.
- Most K. pneumoniae and E. coli without carbapenemases have MICs to imipenem and meropenem that are ≤0.5 mcg/ mL.

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Carbapenems MICs

- Carbapenem MICs for CPKP isolates may vary within a broad range of values (0.12 to >256 mg/L).
- Depends on both the *geographical origin* and *the type of carbapenemase*.
- the EUCAST and the CLSI routine revised their susceptibility breakpoints for carbapenems.

Clin Microbiol Infect 2011; 17: 1135-1141

Breakpoint values of carbapenems: US (CLSI) & European (EUCAST) guidelines

Clin Microbiol Infect 2010; 16: 112–122

Organisms	CLSI		EUCAST	
	S (≤)	R (≥)	S (≤)	R (>)
Enterobacteriaceae				
Imipenem	4	8	2	8
Meropenem	4	8	2	8
Ertapenem	2	4	0.5	1
Doripenem	ND	ND	1	4
Pseudomonas aeruginosa				
Imipenem	4	16	4	8
Meropenem	4	16	2	8
Doripenem	ND	ND	1	4
Acinetobacter spp.				
Imipenem	4	16	2	8
Meropenem	4	16	2	8
Doripenem	ND	ND	1	4

ND, not defined.

Breakpoint values for carbapenems according to the US (CLSI) and European (EUCAST) guidelines, updated June 2010 (MIC values,mg/L)

Clin Microbiol Infect 2012; 18: 432–438

	CLSI		EUCAST	
	S (≤)	R (≥)	S (≤)	R (>)
Imipenem	1	4	2	8
Meropenem	1	4	2	8
Ertapenem	0.5	2	0.5	1
Doripenem	1	4	2	8

Range of MICs of carbapenems for clinical Enterobacteriaceae expressing the main carbapenemases

Clin Microbiol Infect 2012; 18: 432–438

	MIC (mg/L)		
	Imipenem	Meropenem	Ertapenem
KPC	0.5 to >32	0.5 to >32	0.5 to >32
IMP/VIM/NDM	0.5 to >32	0.5 to >64	0.38 to >32
OXA-48/OXA-181	0.25 to 64	0.38 to 64	0.38 to >32

Efficacy of antimicrobial regimens used to treat infections caused by CPKP

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Antibiotic regimen	No. of patients (%)	Outcome success (%)	Failure (%)
Monotherapy			
Colistin	64 (24.2)	35 (54.7)	29 (45.3)
Tigecycline	8 (4.7)	5 (62.5)	3 (37.5)
Aminoglycoside	16 (6.8)	12 (75.0)	4 (25.0)
Carbapenem	23 (9.8)	18 (78.3)	5 (21.7)
Total	111 (47.5)	70 (63.1)	41 (36.9)
Combination therapy			
Two or more active drugs (carbapenem not included)	52 (22.2)	38 (73.1)	14 (26.9)
Two or more active drugs (carbapenem included)	30 (12.8)	28 (93.3)	2 (6,7)
Total	82 (35.0)	66 (80.5)	16 (19.5)
'Inappropriate' therapy	41 (17.5)	23 (56.1)	18 (43.9)
Total	234 (100)	159 (67.9)	75 (32.1)

Comparison of the Activity of a Human Simulated, High-Dose, Prolonged Infusion of **Meropenem** against ***Klebsiella pneumoniae*** Producing the KPC Carbapenemase versus That against *Pseudomonas aeruginosa* in an ***In Vitro*** Pharmacodynamic Model

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Feb. 2010, p. 804–810

Human PK and PD Studies

Clin Microbiol Infect 2011; 17: 1135–1141

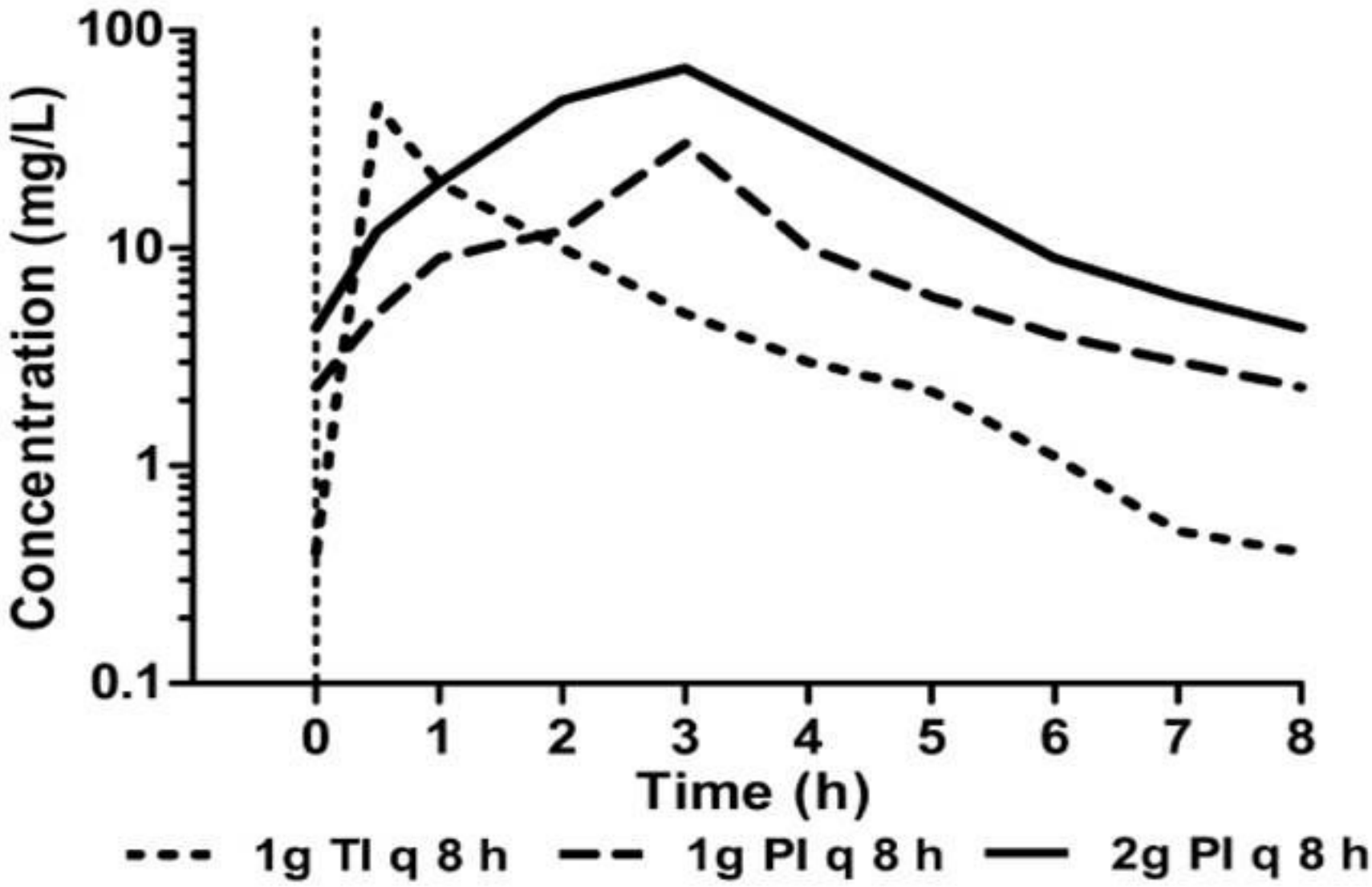

FIG. 1. Simulated concentration–time profiles of three different dosing regimens of meropenem. TI, traditional 30-min infusion; PI, prolonged 3-h infusion. Adapted from [35,45,47].

Human PK and PD Studies

Clin Microbiol Infect 2011; 17: 1135–1141

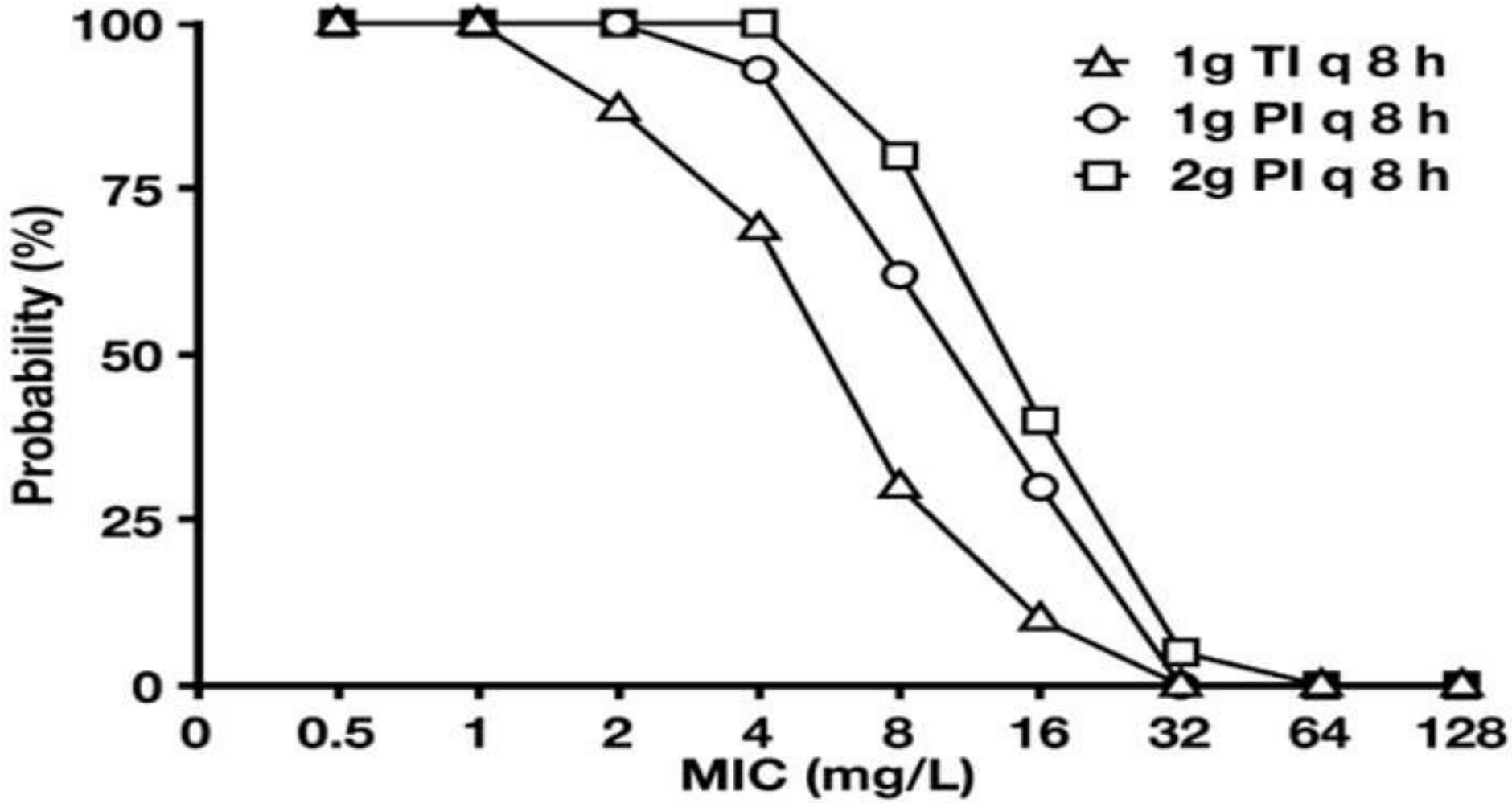

FIG. 2. Simulated target attainment probabilities for 50% time above the MIC (50% *T* > MIC) of three different regiments of meropenem. TI, traditional 30-min infusion; PI, prolonged 3-h infusion. Adapted from [36].

ATTENTION!!

- This is an **in vitro** therapeutic.
- Imipenem is not considered for this therapeutic
- The safety and stability of the compounds.
  - Lower stability at elevated room temperatures.
  - Lower tolerability when administered in higher dosages
- The majority of the patients infected with CPKP isolates are critically ill and have altered renal function

Clin Microbiol Infect 2011; 17: 1135–1141

MDR Gram Negative at Chidren Hospital 2, from Jan 1, 2012 to October 2012

Dr Ngoc Anh, Head of Microbiology Dept

Klebsiella pneumoniae

Kháng sinh	n	nR	nI	nS	%R	%I	%S
Ampicillin	473	473	0	0	100.00 %	0.00%	0.00%
Amikacin	473	32	33	408	6.76%	6.97%	86.25%
Amo/Clavu	473	282	100	91	59.61%	21.14%	19.23%
Piperacillin+Tazo	473	128	89	256	27.06%	18.81%	54.12%
Ticarcilin/A.Clavu	473	308	109	56	65.11%	23.04%	11.83%
Cefotaxime	471	401	10	60	85.13%	2.12%	12.73%
Ceftriaxone	147	104	7	36	70.74%	4.76%	24.48%
Ciprofloxacin	473	212	69	192	44.82%	14.58%	40.59%
Imipenem	473	62	30	381	13.10%	6.34%	80.54%
Ceftazidime	471	315	41	115	66.87%	8.70%	24.41%
Chloramphenicol	444	181	16	247	40.76%	3.60%	55.63%
Gentamicin	473	277	3	193	58.56%	0.63%	40.80%
Levofloxacin	447	172	2	273	38.47%	0.44%	61.07%
Cefoperazone/sul	470	101	91	278	21.48%	19.36%	59.14%
Cefoxitin	471	203	1	267	43.09%	0.21%	56.68%
Ampi(sulbactam)	472	397	25	50	84.11%	5.29%	10.59%
Meropenem	473	59	18	396	12.47%	3.80%	83.72%
Trimetho. (sul)	473	393	8	72	83.08%	1.69%	15.22%
Fosfomycine	144	5	9	130	3.47%	6.250%	90.27%

Acinetobacter spp

Kháng sinh	n	nR	nI	nS	%R	%I	%S
Amikacin	195	60	34	101	30.76%	17.43%	51.79%
Piperacillin+Tazo	190	171	7	12	90.00%	3.68%	6.31%
Ticarcilin/A.Clavu	195	177	5	13	90.76%	2.56%	6.66%
Cefotaxime	190	181	9	0	95.26%	4.73%	0.00%
Cefepime	194	178	1	15	91.75%	0.51%	7.73%
Ciprofloxacin	193	152	3	38	78.75%	1.55%	19.68%
Imipenem	195	166	1	28	85.12%	0.51%	14.35%
Ceftazidime	193	161	6	26	83.41%	3.10%	13.47%
Gentamicin	193	134	20	39	69.43%	10.36%	20.20%
Levofloxacin	189	150	0	39	79.36%	0.00%	20.63%
Cefoperazone/sul	192	159	13	20	82.81%	6.77%	10.41%
Ampi(sulbactam)	194	165	8	21	85.05%	4.12%	10.82%
Meropenem	195	167	0	28	85.64%	0.00%	14.35%
Trimetho. (sul)	191	172	0	19	90.05%	0.00%	9.94%
Fosfomycine	66	60	5	1	90.90%	7.57%	1.51%

CONCLUSION

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