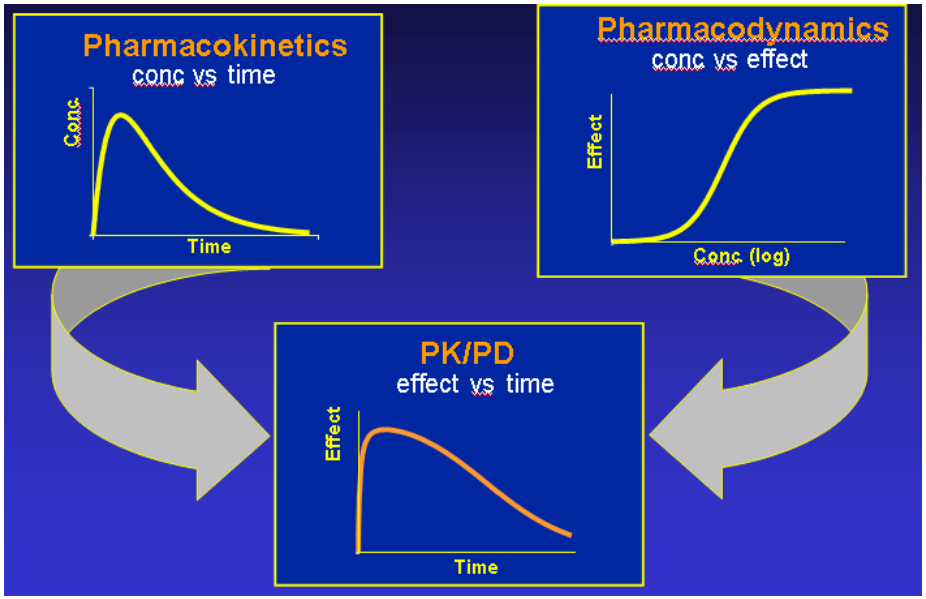
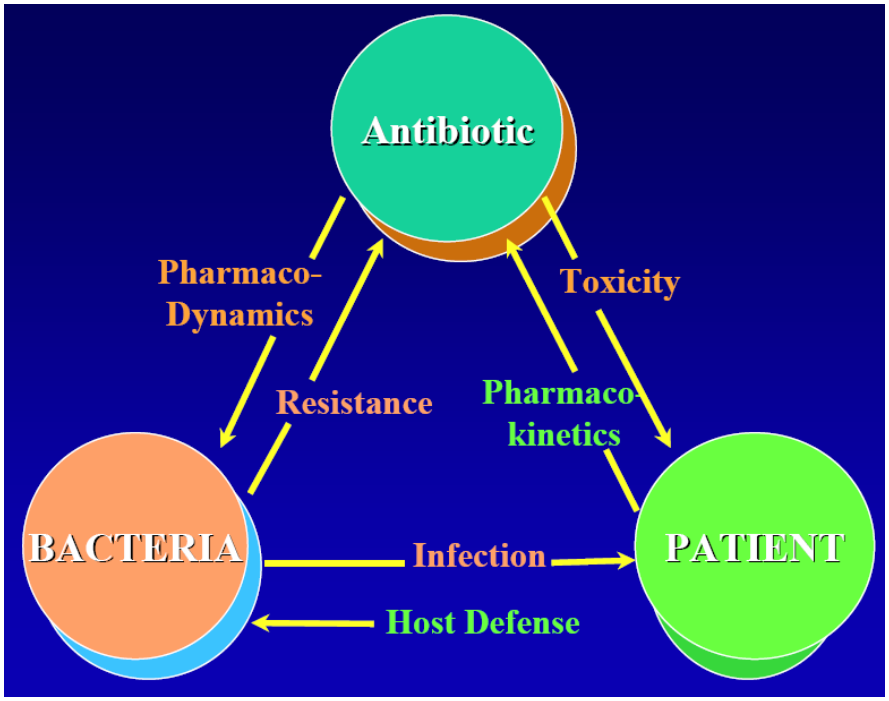
ỨNG DỤNG PK/PD TRONG THỰC HÀNH LÂM SÀNG

Nguyễn Hoàng Anh

Bộ môn Dược lực, Đại học Dược Hà nội





- PK/PD: đánh giá kháng sinh mới cho danh mục thuốc BV
- PK/PD: lựa chọn kháng sinh
- PK/PD: xây dựng hướng dẫn điều trị
- PK-PD: xác định nồng độ đích và lựa chọn chế độ liều cho bệnh nhân nặng

ỨNG DỤNG PK/PD TRONG ĐÁNH GIÁ KHÁNG SINH MỚI: DORIPENEM

Tiêu chí cân nhắc khi lựa chọn kháng sinh

- Chỉ định được phê duyệt và chưa được phê duyệt bởi Cơ quan quản lý Dược phẩm
- ADR
- Dạng bào chế
- Tương tác thuốc-thuốc, thuốc-thức ăn, thuốc-bệnh
- Phổ tác dụng, độ nhạy cảm của vi khuẩn
- Giá thành
- Khả năng phân phối
- Và PK/PD…

Ebert SC. P&T 2004; 29: 244-252.

Tổng hợp thông tin về thuốc dự kiến đưa vào danh mục thuốc bệnh viện cho DTC

1. Tên hoạt chất
2. Tên các biệt dược
3. Các công ty cung cấp/phân phối
4. Phân loại dược lý
5. Chỉ định điều trị được phê duyệt/off-label
6. Các dạng bào chế
7. Dược động học và SKD
8. Liều dùng cho các đối tượng
9. Các TDP và độc tính
10. Thận trọng đặc biệt và CCĐ
11. So sánh: với các thuốc khác, với các phác đồ điều trị khác, các điều kiện đặc biệt khi sử dụng
12. Khuyến cáo cho danh mục thuốc bệnh viện: không giới hạn, dùng có theo dõi, giới hạn sử dụng, dùng có điều kiện, không đưa vào danh mục

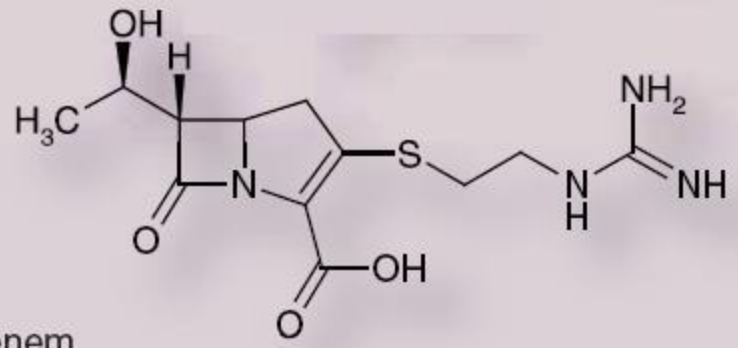
ASHP technical assistance bulletin on the evaluation of drugs for formularies.

DORIPENEM

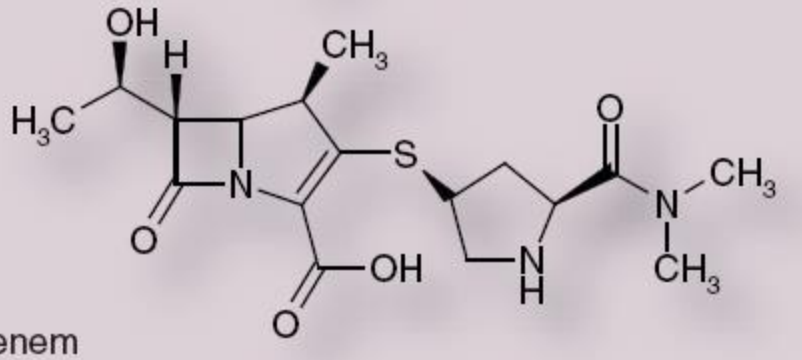
janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

Các kháng sinh carbapenem

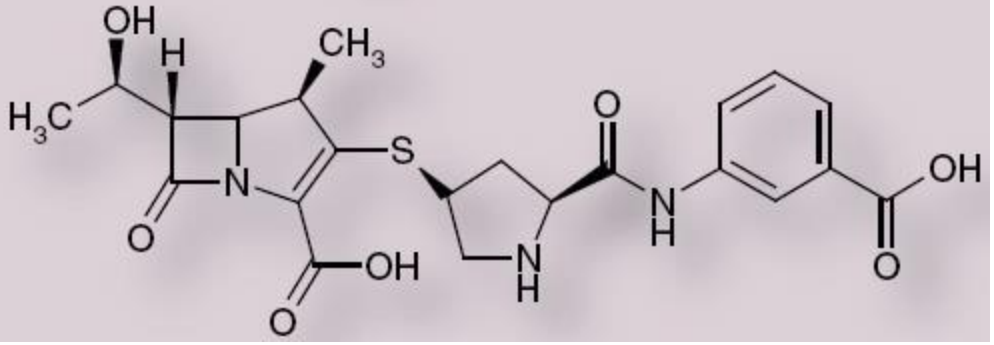
Imipenem



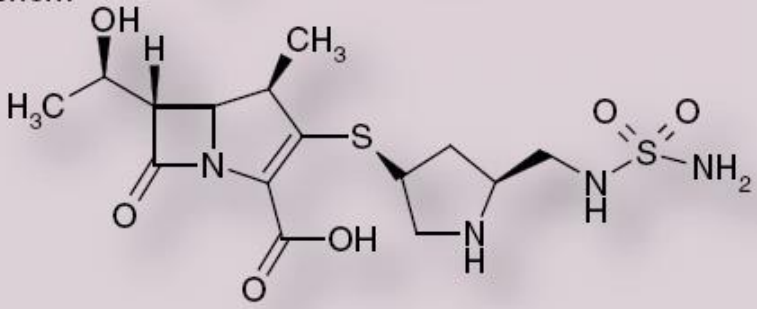
Meropenem



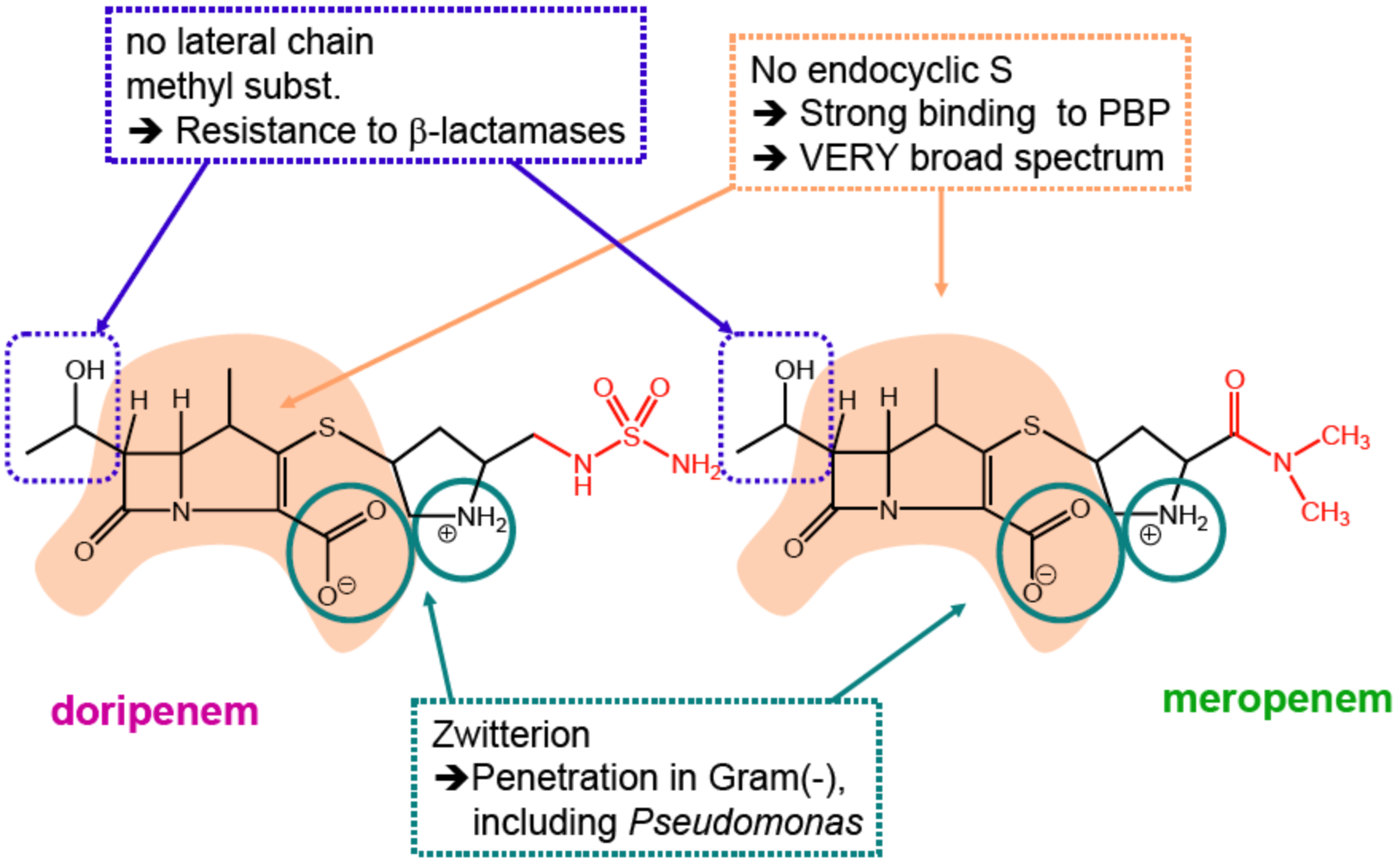
Ertapenem



Doripenem



DORIPENEM VÀ MEROPENEM: CẤU TRÚC HÓA HỌC



HOẠT TÍNH *IN VITRO*

HOẠT TÍNH TRÊN VI KHUẨN GRAM (-)

Pathogen	MIC_{90}, μg/mL		
	Doripenem	Meropenem	Imipenem
Gram negative			
Escherichia coli	0.03	0.016–0.03	0.12–0.25
Klebsiella pneumoniae	0.06–0.12	0.03–0.12	0.25–0.5
Klebsiella oxytoca	0.06	0.03	0.5
Proteus mirabilis	0.5	0.12	4.0
Proteus vulgaris	0.5	0.12	2.0
Morganella morganii	0.25	0.06	2.0
Citrobacter freundii	0.03–0.06	0.03–0.06	0.5–1.0
Enterobacter cloacae	0.06	0.06	0.5
Serratia marcescens	0.25–0.5	0.12	1.0–2.0
Pseudomonas aeruginosa	1.0–2.0	2.0–4.0	2.0–8.0
Stenotrophomonas maltophilia	>32.0	>32.0	>32.0
Burkholderia cepacia	8.0	8.0	32.0
Haemophilus influenzae	0.5	0.25	4.0
Bordetella pertussis	0.5	0.25	1.0
Gram positive			
Streptococcus pneumoniae			
Penicillin susceptible	0.008	0.016	0.008
Penicillin resistant	0.5	0.5	0.25
Staphylococcus aureus			
Methicillin susceptible	0.06	0.12	0.16–0.03
Methicillin resistant	8.0	8.0	8.0
Enterococcus faecalis	4.0	8.0	1.0
Enterococcus faecium	>32.0	>32.0	>32.0

DOR vs IMI

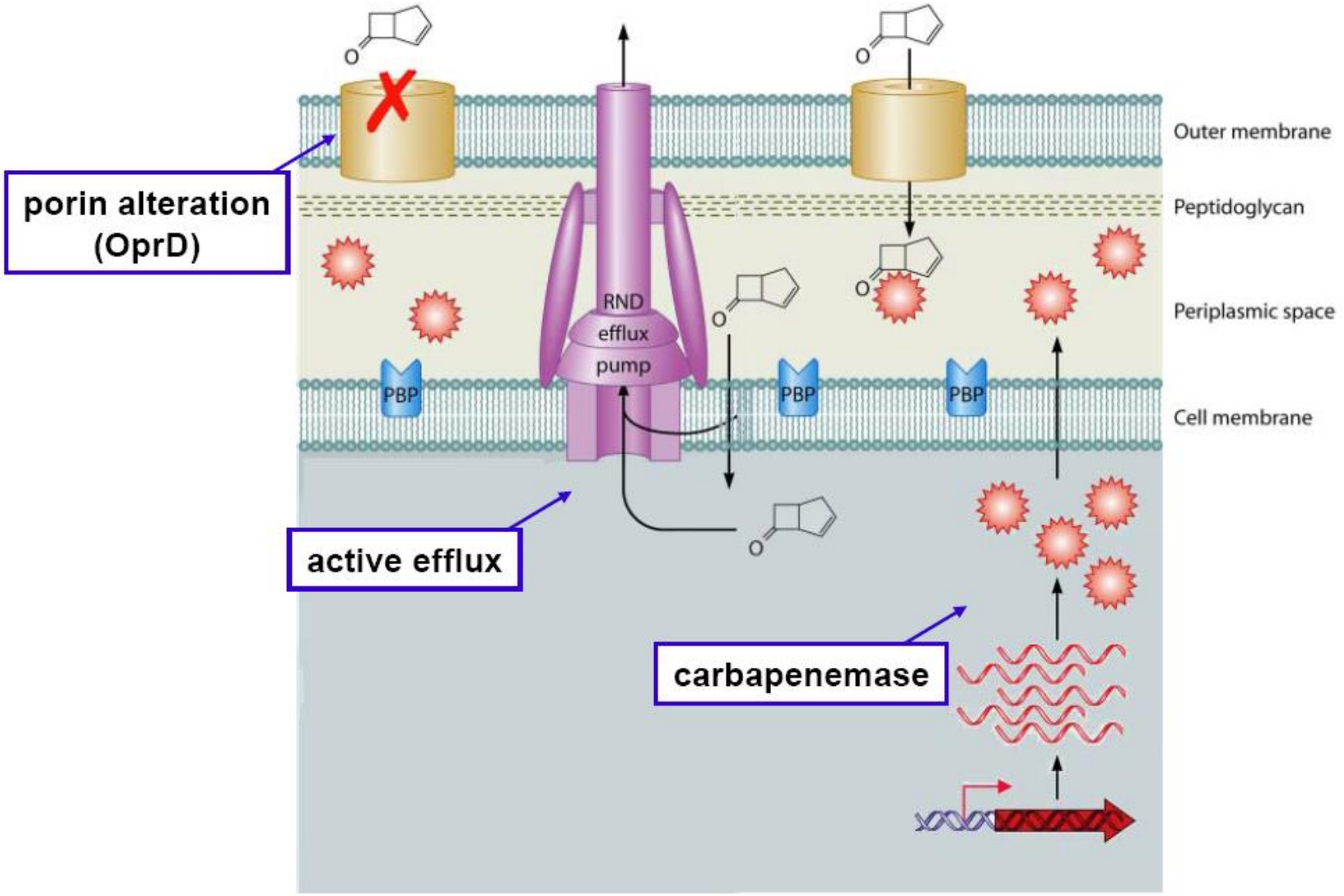
MIC thấp hơn

DOR vs MEM

Khác biệt 1-2 độ pha loãng, lợi thế thường nghiêng về MEM, trừ P.aeruginosa và Gram (+)

Restrepo (2009), CID, 49, S11-16.

CƠ CHẾ ĐỀ KHÁNG CARBAPENEM



Lister et al (2009), Clin. Microbiol. Rev., 22, 582-610

KHẢ NĂNG NHẠY CẢM VỚI CƠ CHẾ KHÁNG THUỐC

Ảnh hưởng của cơ chế đề kháng: *P. aeruginosa*

carbapenem	MexAB	MexEF	OprD	metallo β-lactamase
imipenem	S	r / R	R	R
meropenem	R	R	r	R
doripenem	R	nd	r	R

R : MIC > 8 mg/L
r : MIC < 8 mg/L

Dalhoff et al (2006), Biochem. Pharmacol., 71, 1085-1095.

DƯỢC ĐỘNG HỌC/DƯỢC LỰC HỌC (PK/PD)

DƯỢC ĐỘNG HỌC SO SÁNH

Liều đơn, người tình nguyện

parameter	DOR	MEM	
	(500 mg)	(500 mg)	(1g)
C_{max} (mg/L)	20.2	26	50-60
Prot. binding (%)	8.9	2	
AUC (mg.h/L) – 8 h	44.1	27.2-32.4	66.9-77.5
$T_{½}$ (h)	0.93	1	

Elimination of doripenem is primarily via the renal route

- Dosage adjustment is necessary in patients with moderate and severe renal impairment; AUCs of doripenem and of the microbiologically inactive ring-opened metabolite are substantially increased in patients who require haemodialysis compared with healthy subjects
- the pharmacokinetics of doripenem are not expected to be affected by hepatic impairment.

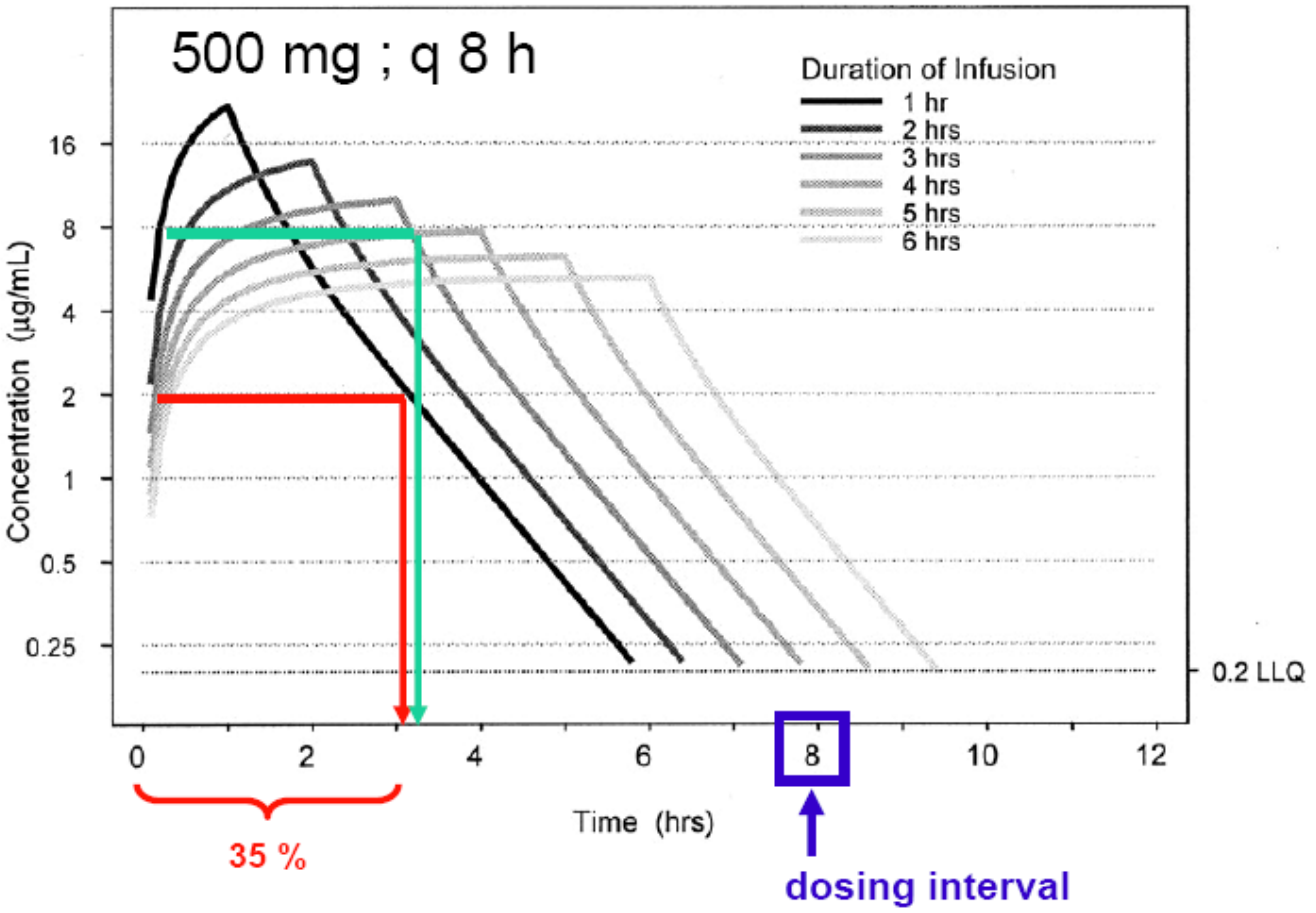
Zhanel et al (2007), Drugs, 67, 1027-1052.

DORIPENEM: MÔ HÌNH HÓA PK/PD

PK/PD in support to dosing : *f* T > MIC ~ 35 %

4 h infusion :
MIC = 8

1 h infusion :
MIC = 2



Bhavnani et al (2005), AAC, 49, 3944-3947.

MEROPENEM: MÔ HÌNH HÓA PK/PD

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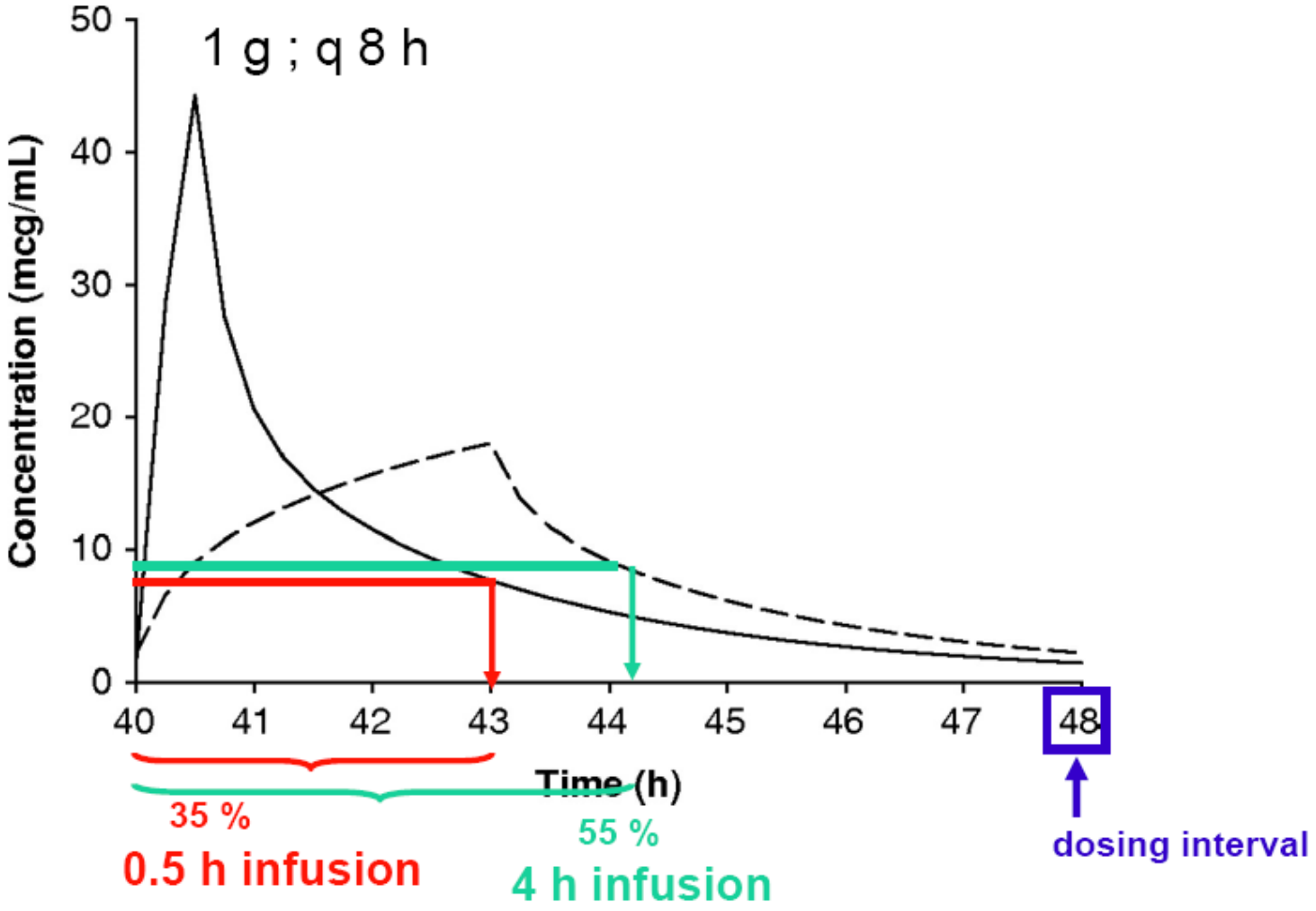
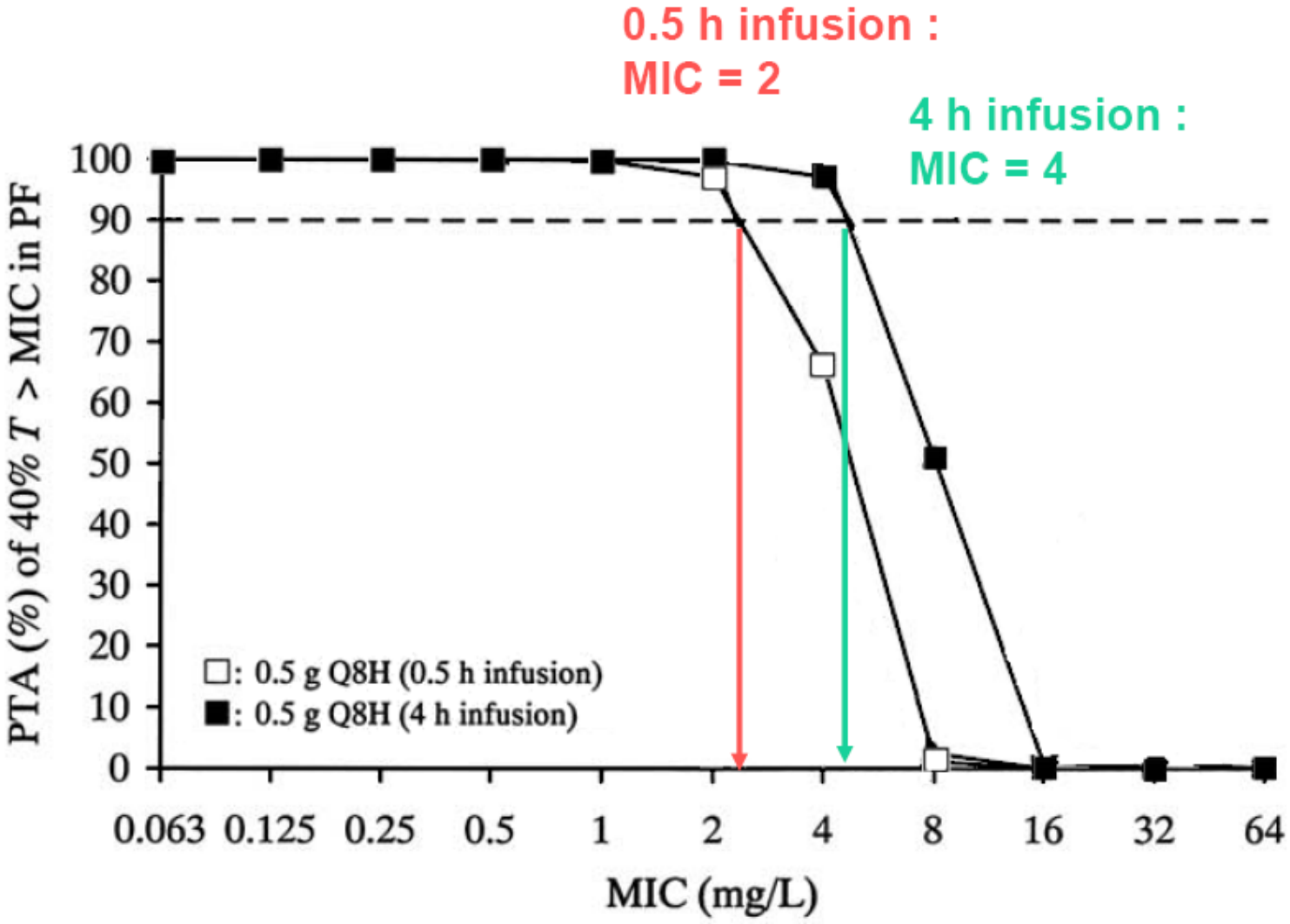


Li et al (2006), J. Clin. Pharmacol., 46, 1171-1178

DORIPENEM: MÔ HÌNH HÓA PK/PD

Probability of target attainment rate based on Monte Carlo simulation



Ikawa et al (2008), Diagn. Microbiol. Infect. Dis., 62, 292-297

MEROPENEM: MÔ HÌNH HÓA PK/PD

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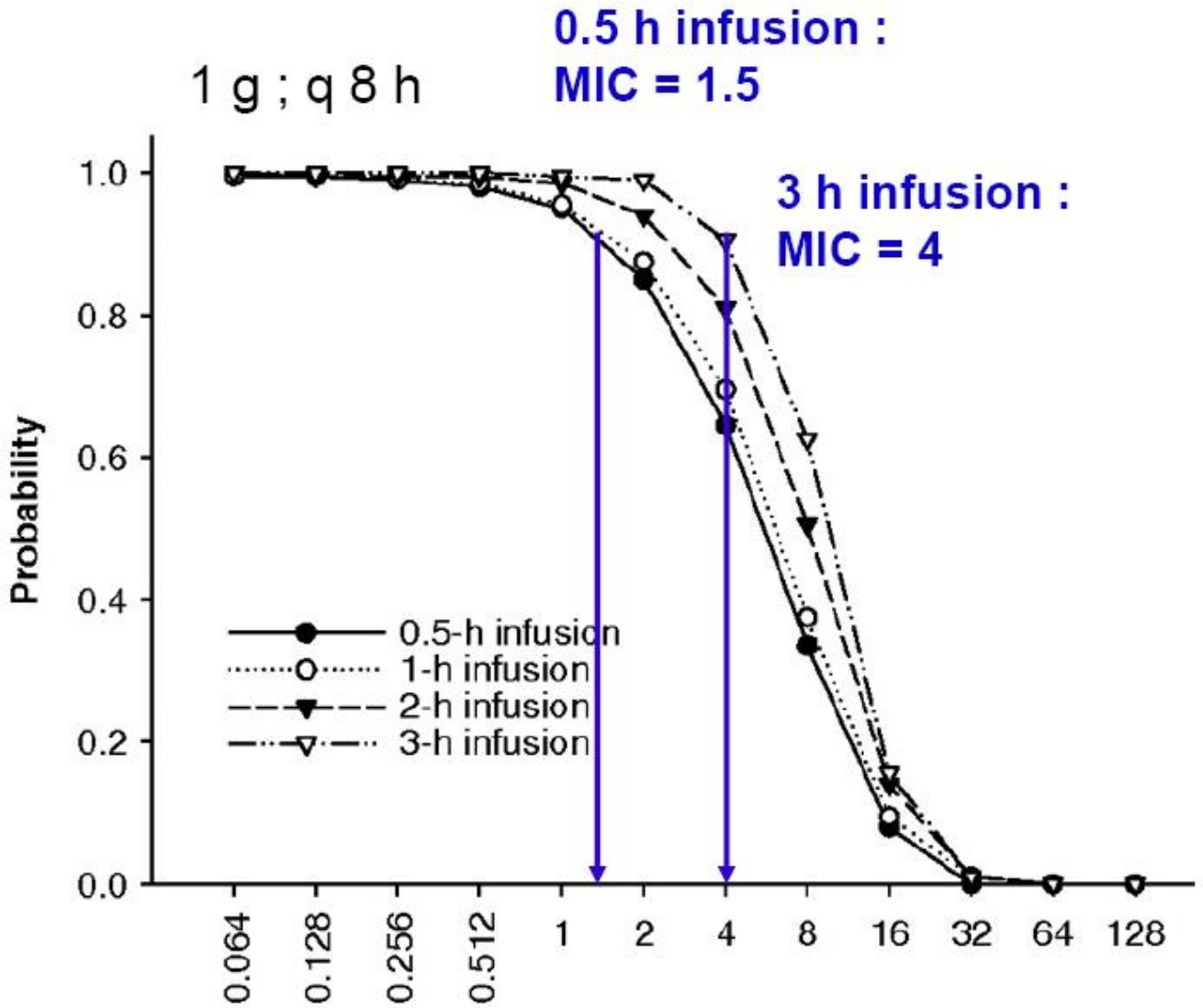

Li et al (2006), J. Clin. Pharmacol., 46, 1171-1178

MEROPENEM/DORIPENEM
MÔ HÌNH HÓA PK/PD SO SÁNH
Bolus vs Prolonged infusion

parameter	DOR (500 mg)		MEM (1g)	
	(Bol)	(Prol)	(Bol)	(Prol)
Cmax (mg/L)	23	8	112	30
AUC (mg.h/L) – 8 h	36	17	136	186
T > CMI 1	55	80	75	98
T > CMI 4	27.5	55	57	73
T > CMI 8	17.5	-	46	58

anticipated success for organisms with MIC for which "*f* T > MIC" ~ 40 % *

anticipated failure for organisms with MIC for which "*f* T > MIC" < 40 % *

* success/failure turn-out in animal models for a "*f* T > MIC" of 35 %

Kim et al (2008), AAC, 52, 2497-2502; Januratanasirikul et al (2005), 49, 1337-1339.

MEROPENEM/DORIPENEM: EUCAST BREAK POINTS

	DOR (500 mg 3 x)	MEM (1 g 3 x)
EUCAST	1 / 4	2 / 8
PD short infusion	2	2
PD prolonged infusion	4	4

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

DORIPENEM: ĐÁNH GIÁ CỦA EUCAST

Specific target attainment rates for organisms obtained in the phase 3 clinical studies

	Dosing regimens used					
	500 mg, q8h, 1 h infusion			500 mg, q8h, 4 h infusion		
Species specific target attainment	**25% T>MIC**	**30% T>MIC**	**35% T>MIC**	**25% T>MIC**	**30% T>MIC**	**35% T>MIC**
Enterobacteriaceae	99.88	99.82	99.72	99.91	99.9	99.9
Non-Enterobacteriaceae	92.34	90.13	87.83	93.96	93.69	93.3
Pseudomonas aeruginosa	91.42	88.96	86.41	93.25	92.95	92.51
Acinetobacter spp.	82.13	80.95	78.99	82.26	82.2	82.16
Other gram-negative	99.43	98.01	96.06	100.02	100.02	100.01
Haemophilus spp.	100	99.97	99.88	100	100	100
Enterococcus faecalis	76.79	62.42	50.79	90.61	89.4	87.18
Staphylococcus aureus Oxa-S	100	100	99.99	100	100	100
Streptococcus pneumoniae	100	99.91	99.7	100.	100.	100.
Streptococcus spp. (other than *S. pneumoniae*)	99.81	99.66	99.54	99.96	99.96	99.93
Other gram-Positive	90.13	89.74	89.02	90.08	90.05	90.03
All Anaerobes	97.75	97.26	96.66	98.09	98	97.89

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

DORIPENEM: PHÊ DUYỆT CỦA EMA

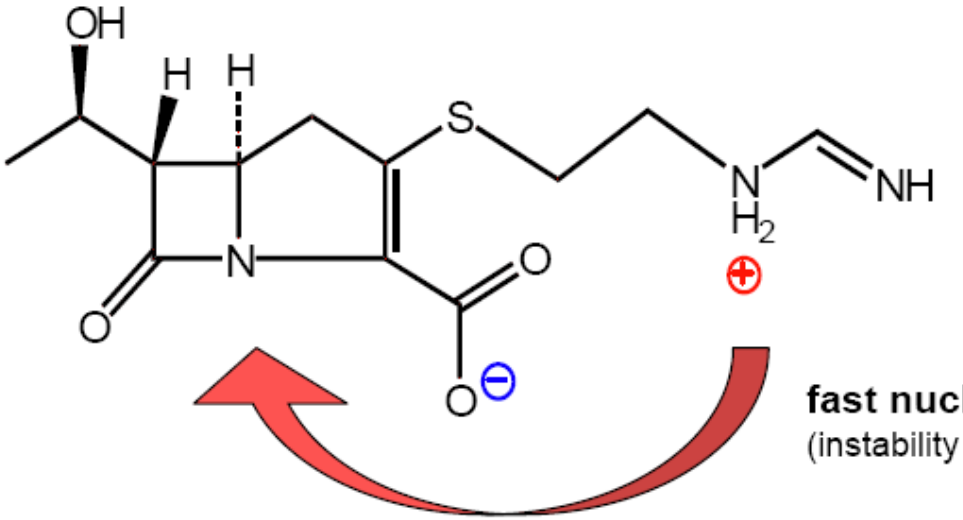
Pharmacokinetic/pharmacodynamic relationship

Similar to other beta-lactam antimicrobial agents, the time that the plasma concentration of doripenem exceeds the MIC (%T>MIC) of the infecting organism has been shown to best correlate with efficacy in pre-clinical pharmacokinetic/pharmacodynamic (PK/PD) studies. Monte Carlo simulations using pathogen susceptibility results from completed phase 3 trials and population PK data indicated that the %T>MIC target of 35% was achieved in greater than 90% of patients with nosocomial pneumonia, complicated urinary tract infections and complicated intra-abdominal infections, for all degrees of renal function.

Extending the infusion time of Doribax to 4 hours maximizes the %T>MIC for a given dose and is the basis for the option to administer 4-hour infusions in patients with nosocomial pneumonia including ventilator-associated pneumonia. In seriously ill patients or those with an impaired immune response, a 4-hour infusion time may be more suitable when the MIC of doripenem for the known or suspected pathogen(s) has been shown or is expected to be > 0.5 mg/l, in order to reach a target attainment of 50% T>MIC in at least 95% of the patients (see section 4.2). Monte Carlo simulations supported the use of 500 mg 4-hour infusions every 8 hours in subjects with normal renal function for target pathogens with doripenem MICs ≤ 4 mg/l.

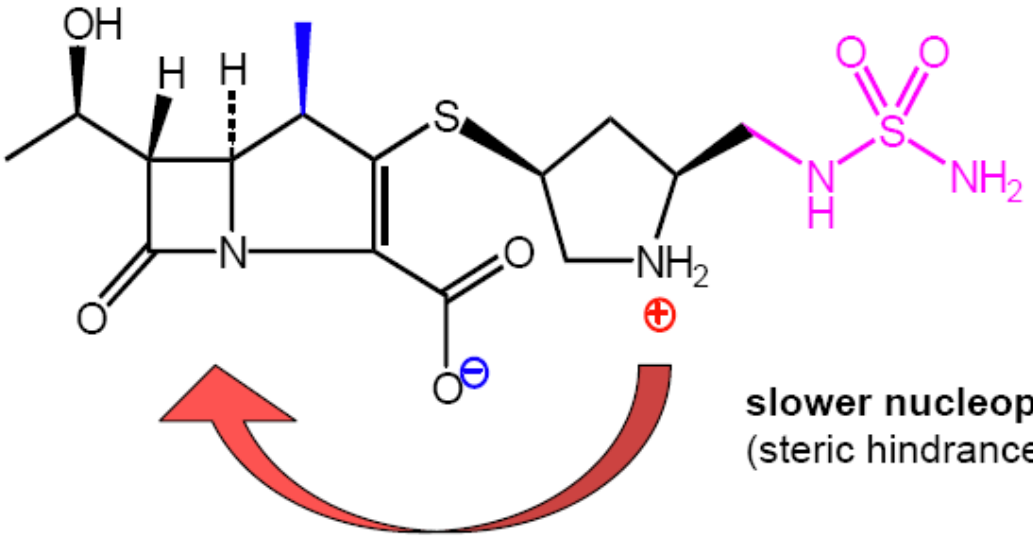
DORIBAX® Summary or Product Characteristics (EMEA)

LIỆU DORIPENEM CÓ BỀN VỮNG VỀ HÓA HỌC ĐỂ TRUYỀN TĨNH MẠCH 4 h?



imipenem

fast nucleophilic attack
(instability of the amidinium function)



doripenem *

slower nucleophilic attack
(steric hindrance)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ĐỘ ỔN ĐỊNH THEO EMA

Preparation of 500 mg dose of solution for infusion

1. Add 10 ml of sterile water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection to the vial and shake it to form a suspension.
2. Inspect the suspension visually for foreign matter. Note: the suspension is not for direct infusion.
3. Withdraw the suspension using a syringe and needle and add it to an infusion bag containing 100 ml of either sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection and mix to complete dissolution. Infuse all of this solution to administer a 500 mg dose of doripenem.

➔ **0.5 % solution… Intensive Care Units may like to put 500 mg in 48 mL (1.048 %)**

Time by which reconstitution, dilution and infusion must complete for Doribax infusion solutions

Infusion solution	Solution stored at room temperature	Solution stored in a refrigerator (2°C-8°C)
sodium chloride 9 mg/ml (0.9%) solution for injection	12 hours	72 hours*
+dextrose 50 mg/ml (5%) solution for injection	4 hours	24 hours*

* Once removed from the refrigerator, infusions should be completed within the room temperature stability time, provided the total refrigeration time, time to reach room temperature and infusion time does not exceed refrigeration stability time.

+ Dextrose 50 mg/ml (5%) solution for injection should not be used for infusion durations greater than 1 hour.

DORIBAX® Summary or Product Characteristics (EMEA)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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+ Dextrose 50 mg/m… for infusion durations greater than 1 hour.

glucose is a good nucleophilic attacker
(a lot of –OH groups…

DORIBAX® Summary or Product Characteristics (EMEA)

ĐỘ ỔN ĐỊNH THEO EMA

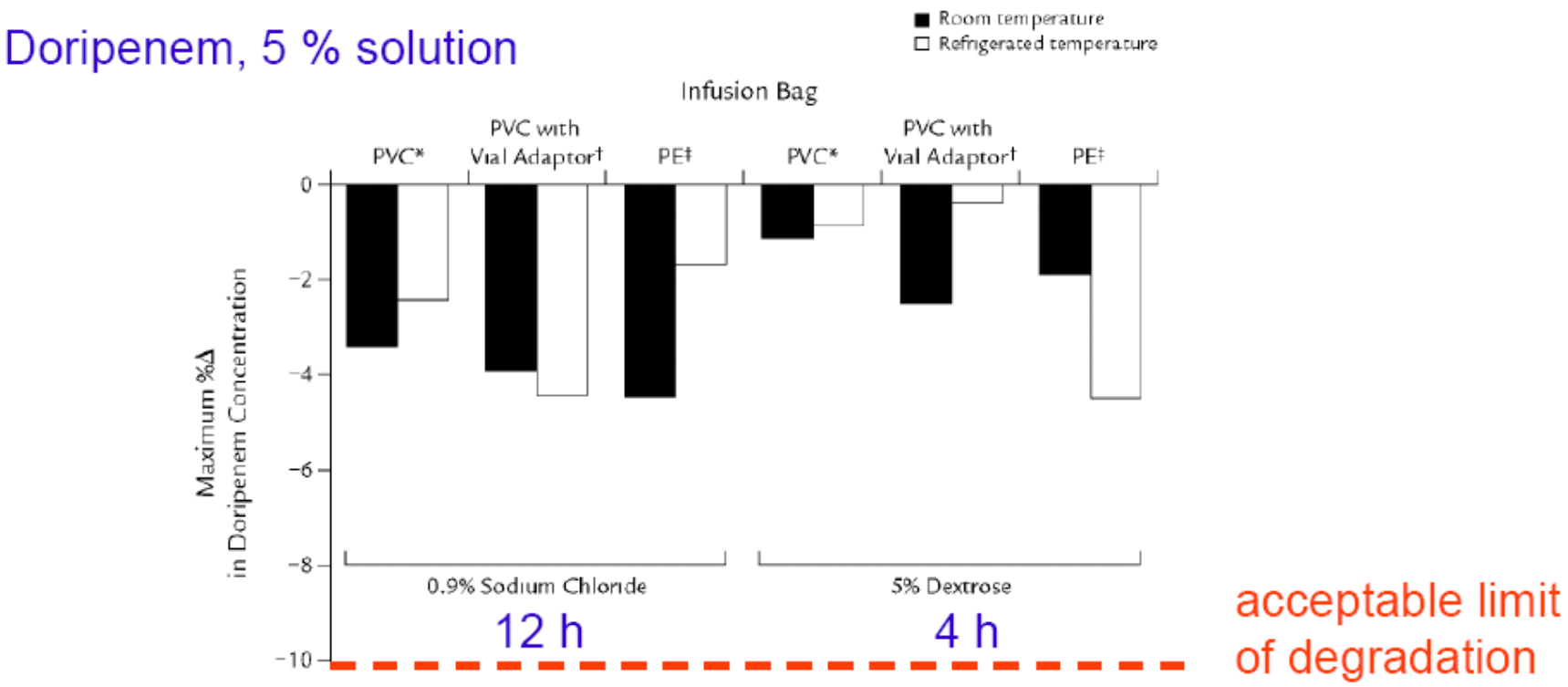

Figure 2. Maximum change in initial (0-hour) doripenem concentration after storage at room or refrigerated temperature. Infusion solutions prepared in 0.9% sodium chloride injection were stored at room temperature (25°C ± 2°C and 60% ± 5% relative humidity for 12 hours under fluorescent light) and at refrigerated temperature (5°C ± 3°C and 60% ± 5% relative humidity for 72 hours protected from light). Solutions prepared in 5% dextrose injection were stored at room and refrigerated temperatures for 4 and 48 hours, respectively. Changes at storage end point are shown. PVC = polyvinyl chloride; PE = polyethylene. *Trademark: Viaflex Mini-Bag (Baxter International Inc., Deerfield, Illinois). †Trademark: Mini-Bag Plus (Baxter International Inc.). ‡Trademark: Viaflo Mini-Bag (Baxter International Inc.).

Pasathas et al (2008), Clin. Ther., 30, 2075-2087

EUROPEAN MEDICINES AGENCY
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ĐỘ ỔN ĐỊNH THEO EMA

TABLE 3. Time during which β-lactams remains >90% stable at the highest concentration tested (see Table 1)

Drug(s)	Time (h, min)[a] at:	
	37°C	25°C
Aztreonam	>24	ND
Piperacillin	21, 40	~30
Piperacillin + tazobactam	>24	⩾72[b]
Azlocillin	>24	⩾72[b]
Mezlocillin	14	46, 30
Ceftazidime	8	24
Cefepime	13	20, 30
Cefpirome	7, 15	23, 40
Imipenem + cilastatin	2, 45	3, 30
Meropenem	1, 50	5, 15
Faropenem	>24	~80

[a] Decays were monitored for 24 h; the slope was calculated by linear regression and used to determine the 90% stability time point. All data were rounded to the closest 15-min value. ND, not determined.

[b] 90% stability for at least 72 h, but the slope was too weak to calculate the 90% intercept value with accuracy from the 24-h decay data.

Viaene et al (2002), AAC, 46, 2327-2332

HIỆU QUẢ LÂM SÀNG

Thử nghiệm lâm sàng với doripenem

Table 1. Overview of doripenem clinical trials.

Study	Indication	Study design	Doripenem dosage	Comparator drug (dosage)	No. of patients randomized	Outcome evaluated
Naber et al. [13]	cUTI	Phase 3, randomized, double-blind, double dummy, multicenter	500 mg every 8 h by 1-h IV infusion	Levofloxacin (250 mg every 24 h by 1-h IV infusion)	753	Microbiological cure rate
Ortho-McNeil-Janssen Pharmaceuticals (unpublished data)	cUTI	Phase 3, open-label, single-arm, multicenter	500 mg every 8 h by 1-h IV infusion	…	426	Microbiological cure rate
Lucasti et al. [14]	cIAI	Phase 3, randomized, double-blind, double dummy, multicenter	500 mg every 8 h by 1-h IV infusion	Meropenem (1 g every 8 h by IV bolus)	476	Clinical cure rate
Malafaia et al. [15]	cIAI	Phase 3, randomized, double-blind, double dummy, multicenter	500 mg every 8 h by 1-h IV infusion	Meropenem (1 g every 8 h by IV bolus)	486	Clinical cure rate
Rea-Neto et al. [16]	NP[a]	Phase 3, randomized, open-label, multicenter	500 mg every 8 h by 1-h IV infusion	Piperacillin-tazobactam (4.5 g every 6 h by 30-min IV infusion)	448	Clinical cure rate
Chastre et al. [17]	VAP[b]	Phase 3, randomized, open-label, multicenter	500 mg every 8 h by 4-h IV infusion	Imipenem (500 mg every 6 h by 30-min IV infusion or 1 g every 8 h by 1-h IV infusion)	531	Clinical cure rate

NOTE. cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; IV, intravenous; NP, nosocomial pneumonia; VAP, ventilator-associated pneumonia.

[a] Including early-onset (but not late-onset) VAP.

[b] Early onset or late onset.

Restrepo (2009), CID, 49, S11-16.

Nhiễm trùng hô hấp

Table IX. Efficacy of intravenous doripenem (DOR) in serious bacterial lower respiratory tract infections. Results of randomized trials that compared DOR with imipenem/cilastin (IPM),[129] meropenem (MEM)[127] or piperacillin/tazobactam (TZP)[126] in patients (pts) with nosocomial pneumonia (including one trial[129] in pts with ventilator-associated pneumonia [VAP][126,129] or other serious lower respiratory tract infections.[127] Study drugs were administered intravenously

Study	No. of pts randomized	Treatment regimen	Planned treatment duration (d)	Response rates (% pts) [evaluable pts]			
				clinical response	between-group difference (95% CI)	bacteriological response	between-group difference (95% CI)
Nosocomial pneumonia, including VAP							
Chastre et al.[129]	264	DOR 500 mg q8h infused over 4h	7–14	68.3[a] [126]	3.5 (−9.1, 16.1)[b]	73.3[c] [116]	6.0 (−6.8, 18.8)
	267	IPM 500 mg q6h or 1000 mg q8h infused over 30 or 60 min	7–14	64.8[a] [122]		67.3[c] [110]	
Réa-Neto et al.[126]	225	DOR 500 mg q8h infused over 60 min[d]	7–14	81.3[a] [134]	1.5 (−9.1, 12.1)[e]	84.5[c] [84]	3.8 (−8.9, 16.5)
	223	TZP 4.5 g q6h infused over 30 min[d]	7–14	79.8[a] [119]		80.7[c] [83]	
Other serious lower respiratory tract infections							
Saito et al.[127]	112	DOR 250 mg bid infused over 30–60 min	7	92.7[f] [96]	2.0 (−5.8, 9.8)[g]	86.0 [43]	−9.8 (−21.6, 2.0)
	107	MEM 500 mg bid infused over 30–60 min	7	90.7[f] [97]		95.8 [48]	

Keam (2008), Drugs, 68: 2021-2057.

Nhiễm trùng hô hấp

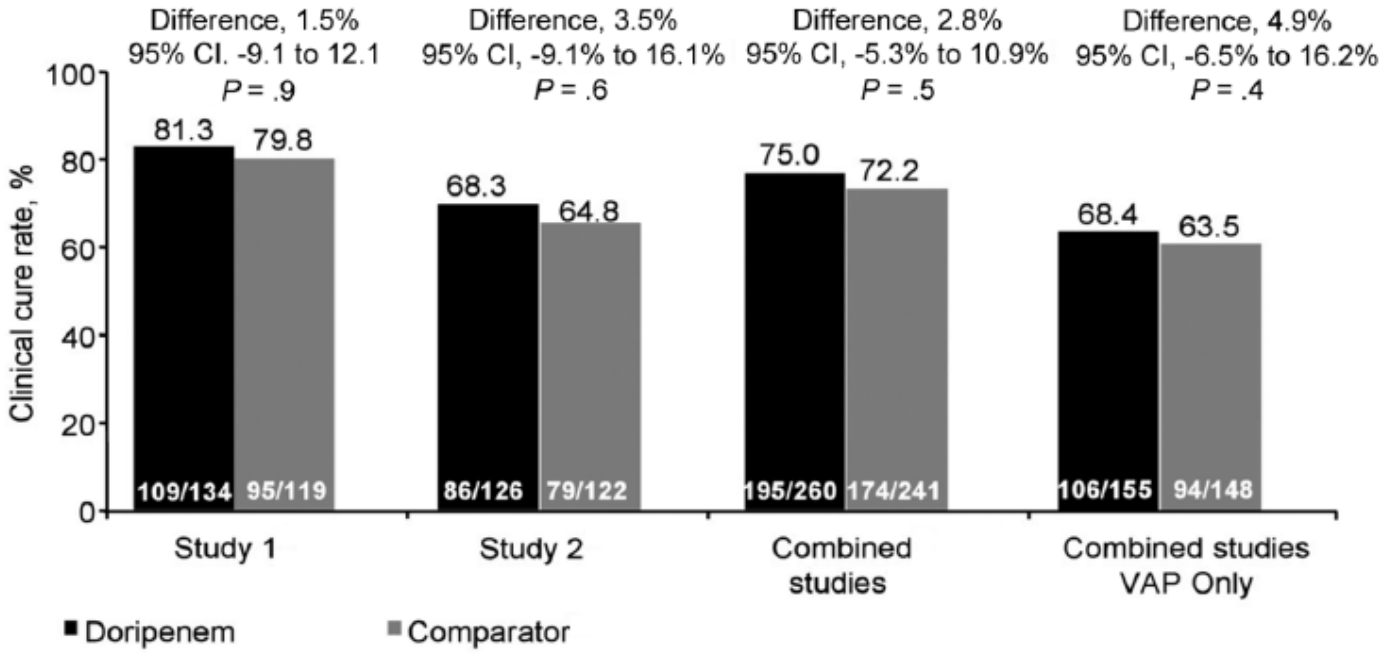


Figure 1. Clinical cure rates among clinically evaluable patients with nosocomial pneumonia, including ventilator-associated pneumonia (VAP). In study 1 [16], doripenem was compared with piperacillin-tazobactam. In study 2 [17], doripenem was compared with imipenem. Data for combined studies are from Chastre et al. [20]. All data are from Ortho-McNeil-Janssen Pharmaceuticals. CI, confidence interval.

Restrepo (2009), CID, 49, S11-16.

Nhiễm trùng hô hấp

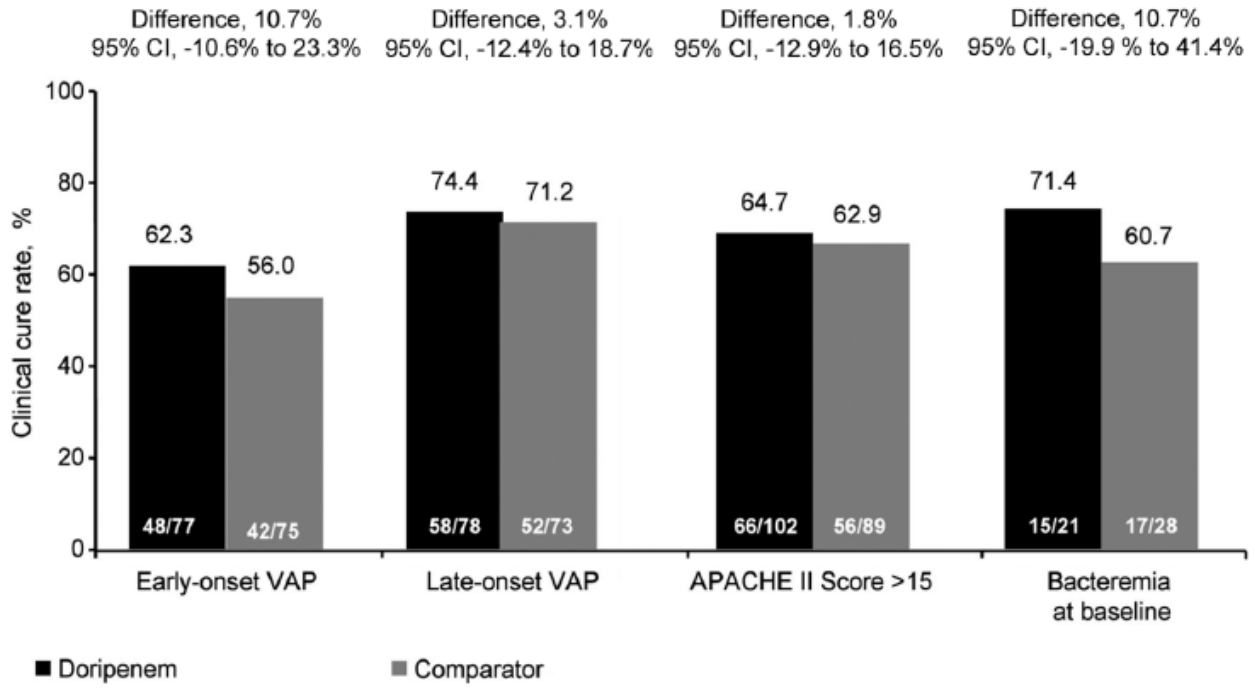


Figure 2. Clinical cure rates among clinically evaluable patients with serious nosocomial pneumonia, including ventilator-associated pneumonia (VAP), in combined studies. In study 1 [16], doripenem was compared with piperacillin-tazobactam. In study 2 [17], doripenem was compared with imipenem. Data are from Ortho-McNeil-Janssen Pharmaceuticals. APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval.

Restrepo (2009), CID, 49, S11-16.

Nhiễm trùng hô hấp

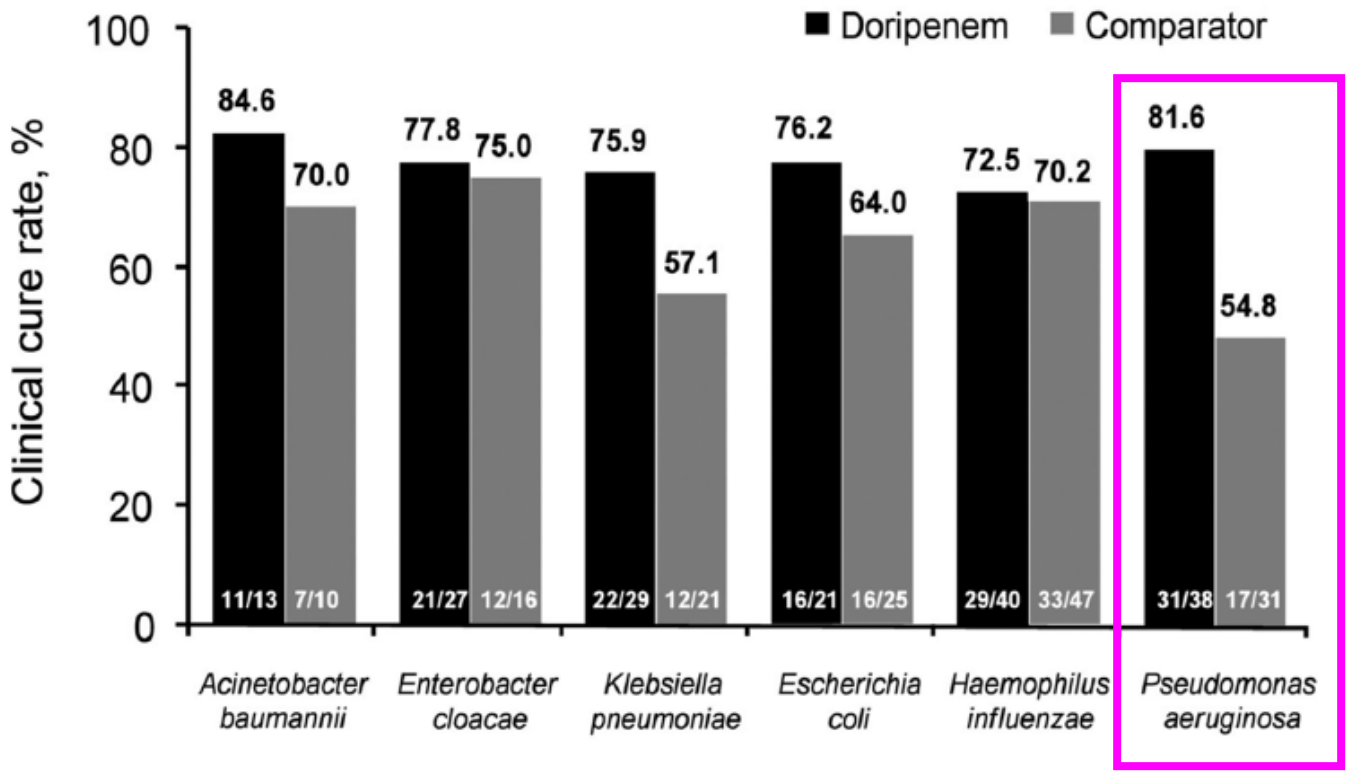


Figure 3. Pooled clinical cure rates, by pathogen, among microbiologically evaluable patients with nosocomial pneumonia, including ventilator-associated pneumonia, in the combined studies. In study 1 [16], doripenem was compared with piperacillin-tazobactam. In study 2 [17], doripenem was compared with imipenem. Data are from Ortho-McNeil-Janssen Pharmaceuticals.

Restrepo (2009), CID, 49, S11-16.

Nhiễm trùng hô hấp

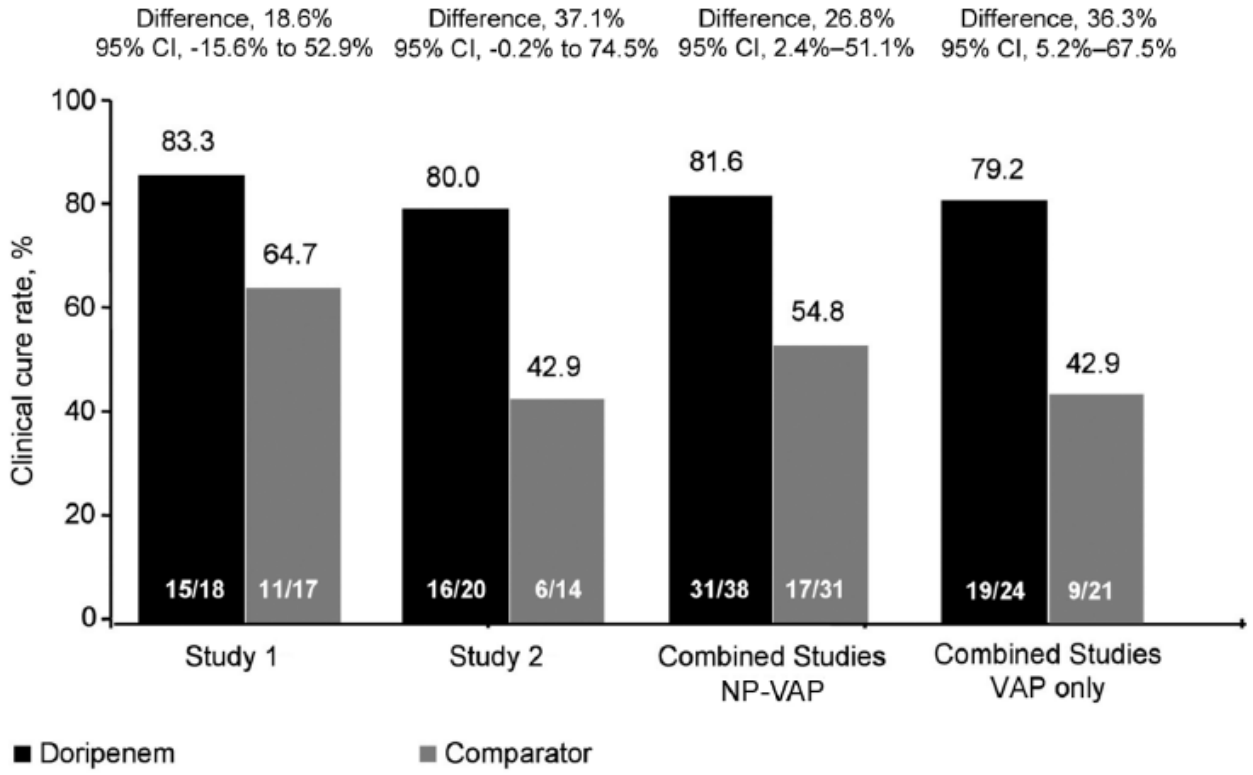


Figure 4. Clinical cure rates among microbiologically evaluable patients infected with *Pseudomonas aeruginosa*. In study 1 [16], doripenem was compared with piperacillin-tazobactam. In study 2 [17], doripenem was compared with imipenem. Data for combined studies are from Chastre et al. [20]. All data are from Ortho-McNeil-Janssen Pharmaceuticals. CI, confidence interval; NP, nosocomial pneumonia; VAP, ventilator-associated pneumonia.

Restrepo (2009), CID, 49, S11-16.

Nhiễm trùng ổ bụng

Design

Patients with IAI, surgical intervention < 24 h + AB needed

exclusion :
- uncomplicated infections
- APACHE II > 30
- life-threatening illness
- necrotizing pancreatitis / pancreatic abcess
- infection by pathogen R to one of the studied drugs

Patients profile

91 % APACHE II < 10
60 % appendix; 20 % colon
10 % post-operative

Treatment

DOR 500 mg x 3; 1h ***vs*** MEM 1 g x 3 ; 5 minutes

Lucasti et al., Clin. Ther (2008) 30:868-83

Nhiễm trùng ổ bụng

Microbiology

Table III. Microorganisms isolated from microbiological modified intent-to-treat patients in this noninferiority study of IV doripenem versus meropenem in adults with complicated intra-abdominal infection. Values are no. (%) of patients.

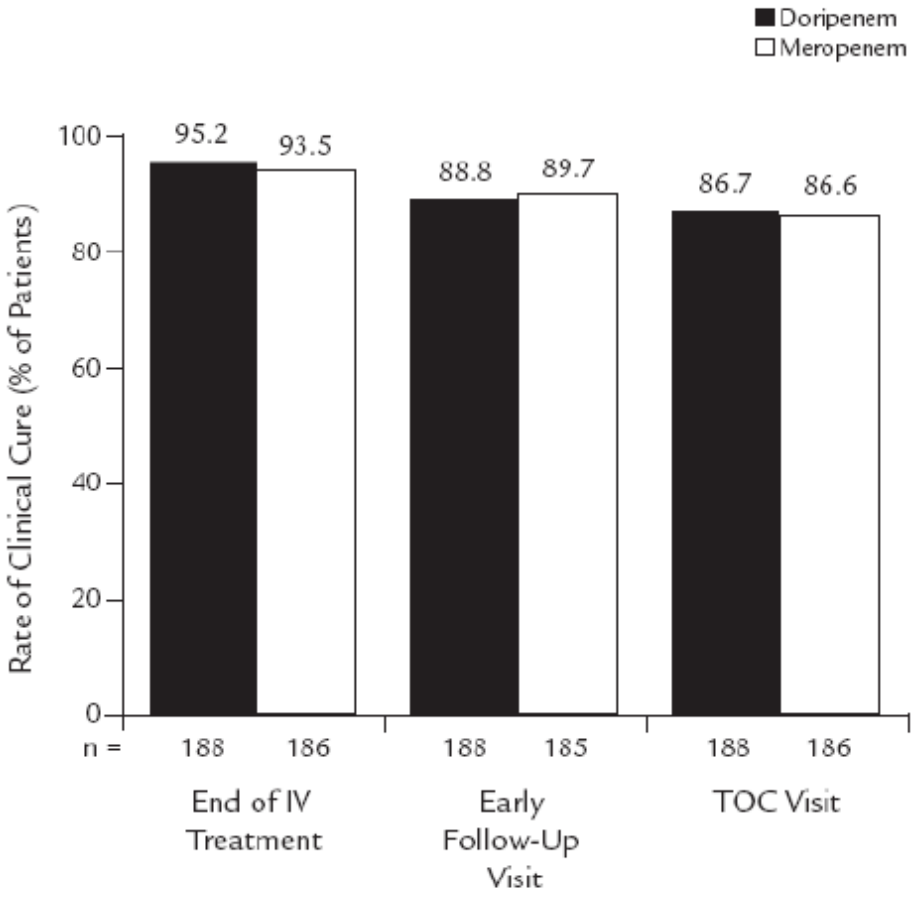
Microorganism	Doripenem (n = 195)	Meropenem (n = 190)
Gram-negative aerobes		
Escherichia coli	121 (62.1)	115 (60.5)
Pseudomonas aeruginosa	22 (11.3)	21 (11.1)
Klebsiella pneumoniae	18 (9.2)	14 (7.4)
Citrobacter spp	18 (9.2)	6 (3.2)
Enterobacter spp	9 (4.6)	10 (5.3)
Proteus spp	8 (4.1)	13 (6.8)
Other *Klebsiella* spp	6 (3.1)	6 (3.2)
Other *Pseudomonas* spp	2 (1.0)	4 (2.1)
Other	13 (6.7)	13 (6.8)
Gram-negative anaerobes		
Bacteroides fragilis	33 (16.9)	28 (14.7)
Other *Bacteroides* spp	20 (10.3)	39 (20.5)
Bacteroides thetaiotaomicron	20 (10.3)	22 (11.6)
Prevotella spp	19 (9.7)	18 (9.5)
Bacteroides caccae	15 (7.7)	8 (4.2)
Bacteroides uniformis	11 (5.6)	15 (7.9)

Microorganism	Doripenem (n = 195)	Meropenem (n = 190)
Gram-negative anaerobes (continued)		
Fusobacterium spp	9 (4.6)	7 (3.7)
Other	5 (2.6)	7 (3.7)
Gram-positive aerobes		
Other *Streptococcus* spp	43 (22.1)	49 (25.8)
Streptococcus viridans group	22 (11.3)	15 (7.9)
Streptococcus intermedius	21 (10.8)	15 (7.9)
Enterococcus faecalis	20 (10.3)	14 (7.4)
Other *Enterococcus* spp	11 (5.6)	16 (8.4)
Staphylococcus aureus	8 (4.1)	12 (6.3)
Other *Staphylococcus* spp	8 (4.1)	10 (5.3)
Enterococcus faecium	6 (3.1)	12 (6.3)
Other	4 (2.1)	2 (1.1)
Gram-positive anaerobes		
Peptostreptococcus spp	13 (6.7)	16 (8.4)
Clostridium spp	10 (5.1)	9 (4.7)
Other	18 (9.2)	16 (8.4)

Lucasti et al., Clin. Ther (2008) 30:868-83

Nhiễm trùng ổ bụng

Clinical success



Lucasti et al.. Clin. Ther (2008) 30:868-83

Nhiễm trùng ổ bụng

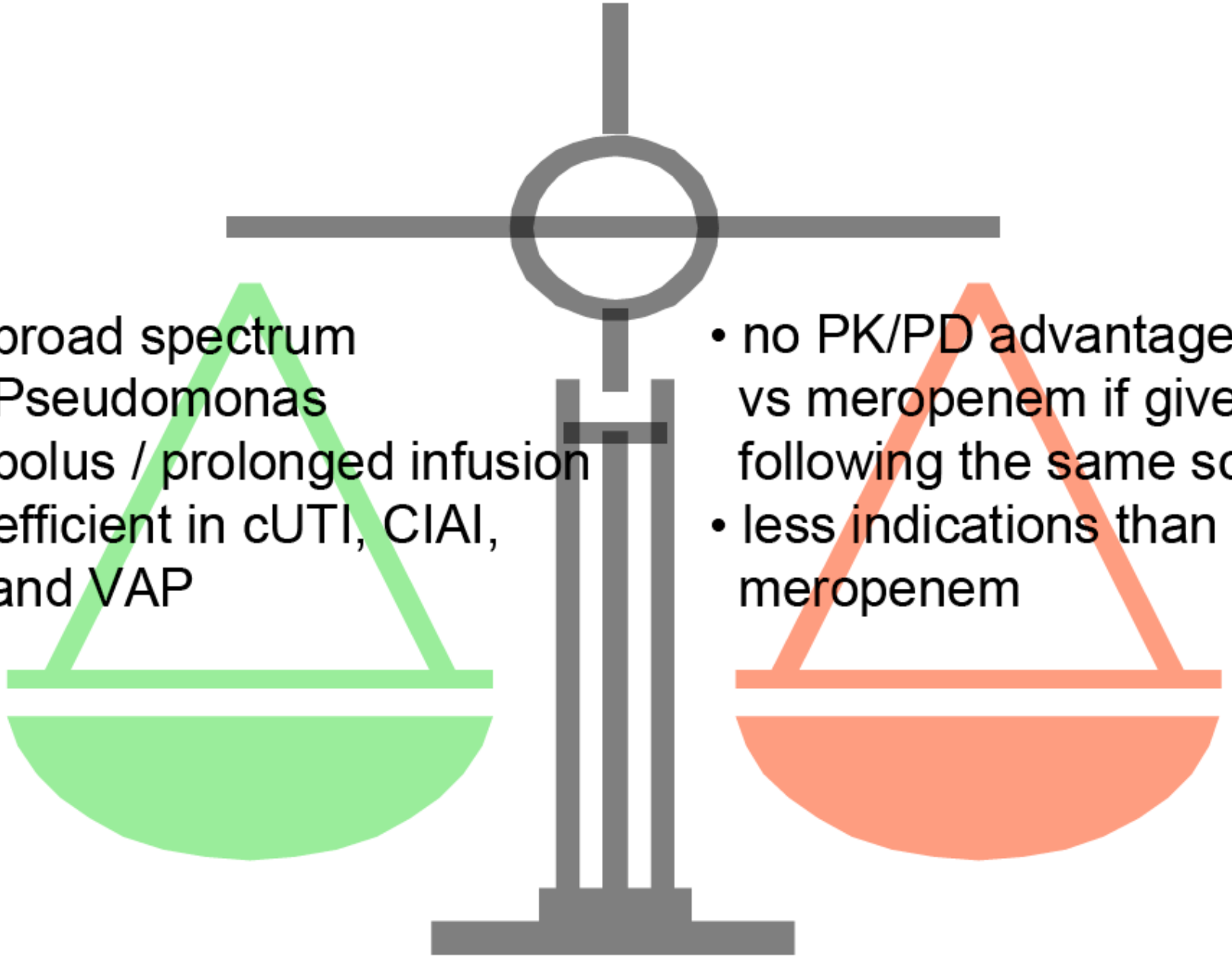
Microbiological evaluation

Table V. Favorable microbiological outcomes for selected baseline intra-abdominal pathogens in the microbiologically evaluable patients in this noninferiority study of IV doripenem versus meropenem in adults with complicated intra-abdominal infection.

	No. (%)		
Pathogen	Doripenem	Meropenem	Difference, %*
Gram-positive aerobes			
Viridans group streptococci	50/54 (92.6)	35/41 (85.4)	7.2
Streptococcus intermedius	15/16 (93.8)	8/10 (80.0)	13.8
Other	27/33 (81.8)	32/38 (84.2)	−2.4
Enterococcus fecalis	9/12 (75.0)	8/9 (88.9)	−13.9
Gram-positive anaerobes	27/33 (81.8)	30/37 (81.1)	0.7
Gram-negative aerobes			
Enterobacteriaceae	140/157 (89.2)	122/141 (86.5)	2.6
Escherichia coli	91/104 (87.5)	84/100 (84.0)	3.5
Klebsiella pneumoniae	14/15 (93.3)	9/9 (100)	−6.7
Nonfermenters	22/23 (95.7)	17/24 (70.8)	24.8
Pseudomonas aeruginosa	18/19 (94.7)	15/19 (78.9)	15.8
Gram-negative anaerobes			
Bacteroides fragilis group	67/75 (89.3)	75/89 (84.3)	5.1
B fragilis	23/27 (85.2)	16/22 (72.7)	12.5
Bacteroides thetaiotaomicron	14/16 (87.5)	19/20 (95.0)	−7.5
Bacteroides caccae	11/12 (91.7)	8/8 (100)	−8.3
Bacteroides uniformis	10/11 (90.9)	8/11 (72.7)	18.2
Other	21/27 (77.8)	28/30 (93.3)	−15.6

Lucasti et al., Clin. Ther (2008) 30:868-83

Doripenem : pros and cons



- broad spectrum
- Pseudomonas
- bolus / prolonged infusion
- efficient in cUTI, CIAI, and VAP

- no PK/PD advantage vs meropenem if given following the same scheme
- less indications than meropenem

ỨNG DỤNG PK/PD TRONG LỰA CHỌN KHÁNG SINH: VÍ DỤ FLUOROQUINOLON

LỰA CHỌN KHÁNG SINH FLUOROQUINOLON TRONG THỰC HÀNH

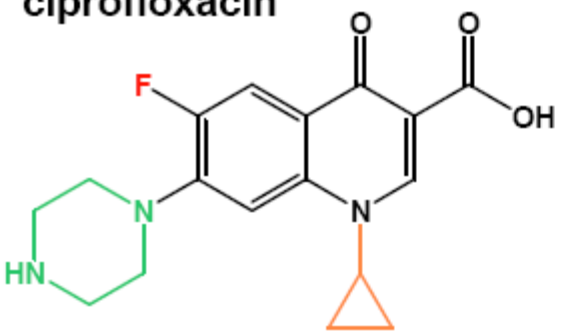
Is More Than One Quinolone Needed in Clinical Practice?

Joseph A Paladino

Ann Pharmacother 2001;35:1085-95.

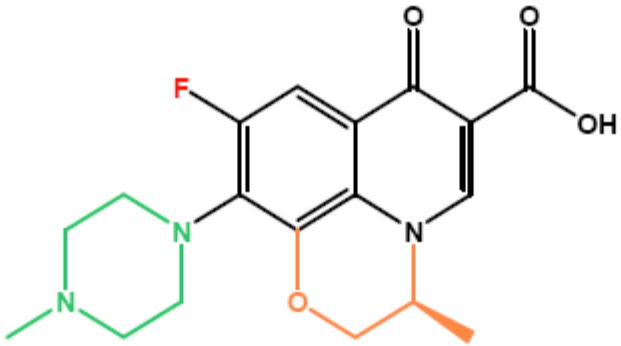
PHÁT TRIỂN NHÓM KHÁNG SINH FLUOROQUINOLON

ciprofloxacin



substituents contributing
to increase in potency

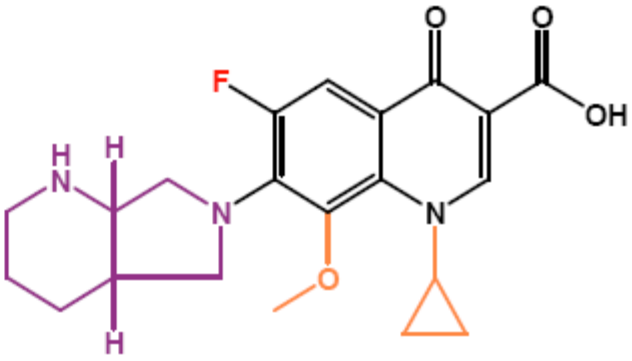
levofloxacin



Gram(-)

Gram(+)

moxifloxacin



DƯỢC ĐỘNG HỌC SO SÁNH 3 KHÁNG SINH QUINOLON

	Ciprofloxacin	Levofloxacin	Moxifloxacin
F (%)	70-80	99	90
LK protein HT (%)	30-40	30-40	50
% thải qua thận dạng nguyên vẹn	30	95	15
t1/2 (h)	3	8	12
Ức chế CYP450	Có	Không	Không

➡ **Khác biệt về**

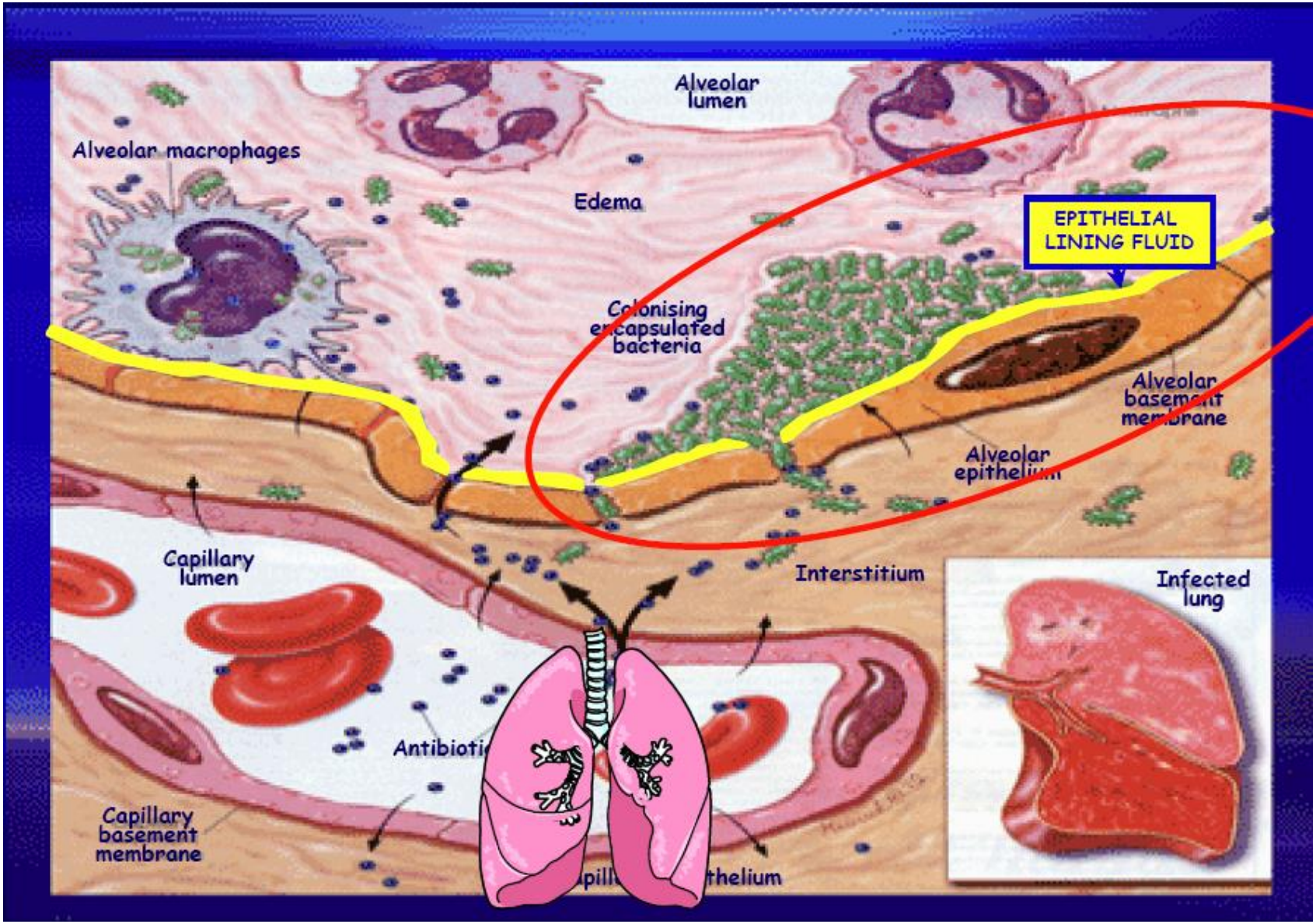
- Số lần dùng/ngày
- Hiệu chỉnh liều
- Tương tác thuốc

TÓM TẮT HOẠT TÍNH TRÊN VI KHUẨN CỦA 3 KHÁNG SINH FLUOROQUINOLON

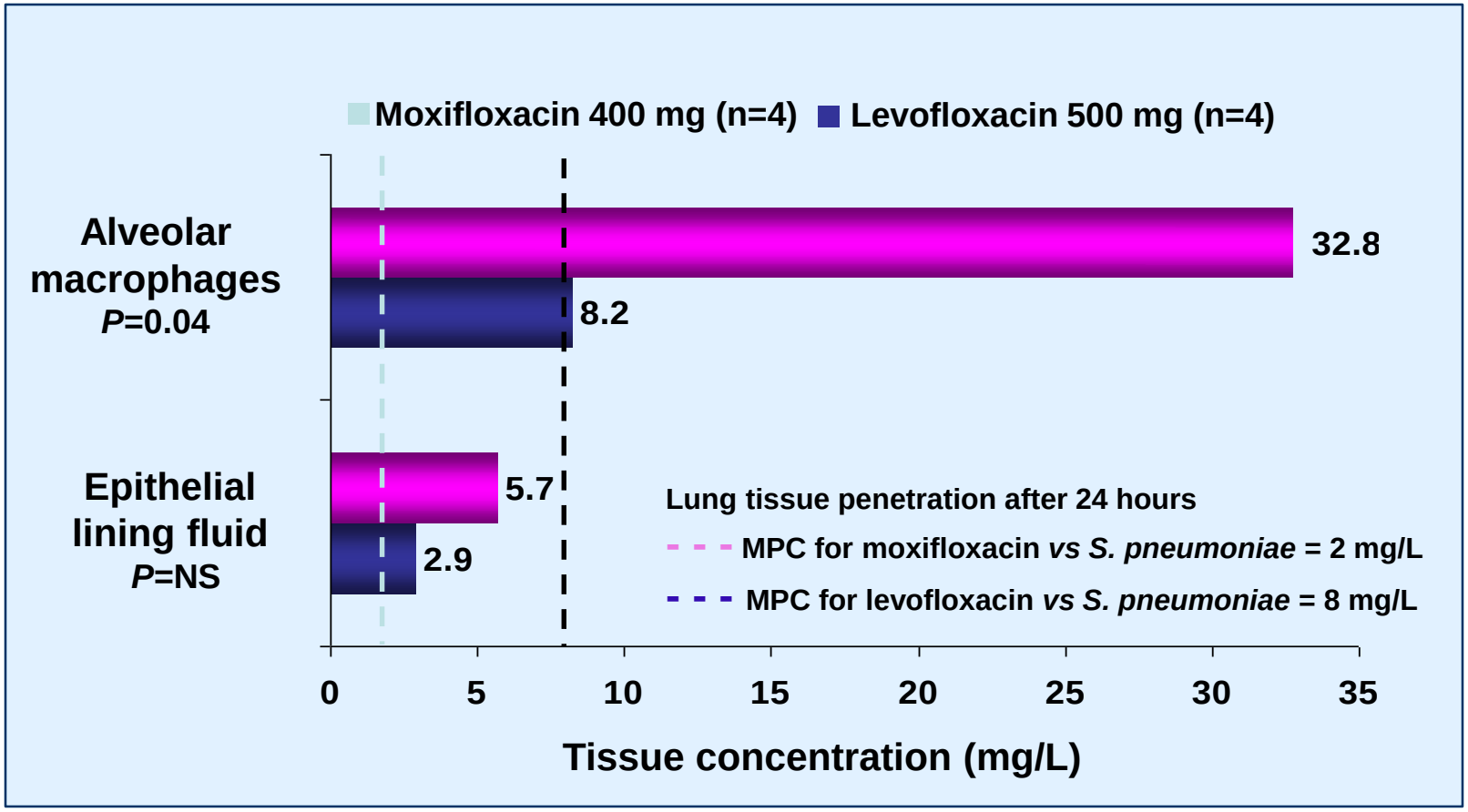
S. pneumoniae	**Moxifloxacin > ciprofloxacin or levofloxacin**
H. influenzae	**Moxifloxacin = ciprofloxacin = levofloxacin**
M. catarrhalis	**Moxifloxacin = ciprofloxacin = levofloxacin**
Chủng viêm phổi cộng đồng không điển hình	**Moxifloxacin > levofloxacin > ciprofloxacin**
P. aeruginosa	**Ciprofloxacin > levofloxacin > moxifloxacin**
E. coli	**Ciprofloxacin > levofloxacin**
K. pneumoniae	**Ciprofloxacin > levofloxacin**

1) Blondeau. *J Antimicrob Chemother* 1999; **43(Suppl B)**: 1–11; 2) Dalhoff *et al. Eur J Clin Microbiol Infect Dis* 2003; **22**: 203–21; 3) Takahata *et al. Antimicrob Agents Chemother* 2001; **45**: 312–15; 4) Miyashita *et al. J Infect Chemother* 2002; **8**: 115–17; 5) Van Eldere. *J Antimicrob Chemother* 2003; **51**: 347–52; 6) Blondeau *et al. Int J Antimicrob Agents* 2003; **22**: 147–54; 7) CIPRO® tablets US prescribing information, 2011

PK/PD ÁP DỤNG LỰA CHỌN FLUOROQUINOLON: PHÂN BỐ CỦA KHÁNG SINH VÀO VỊ TRÍ NHIỄM TRÙNG



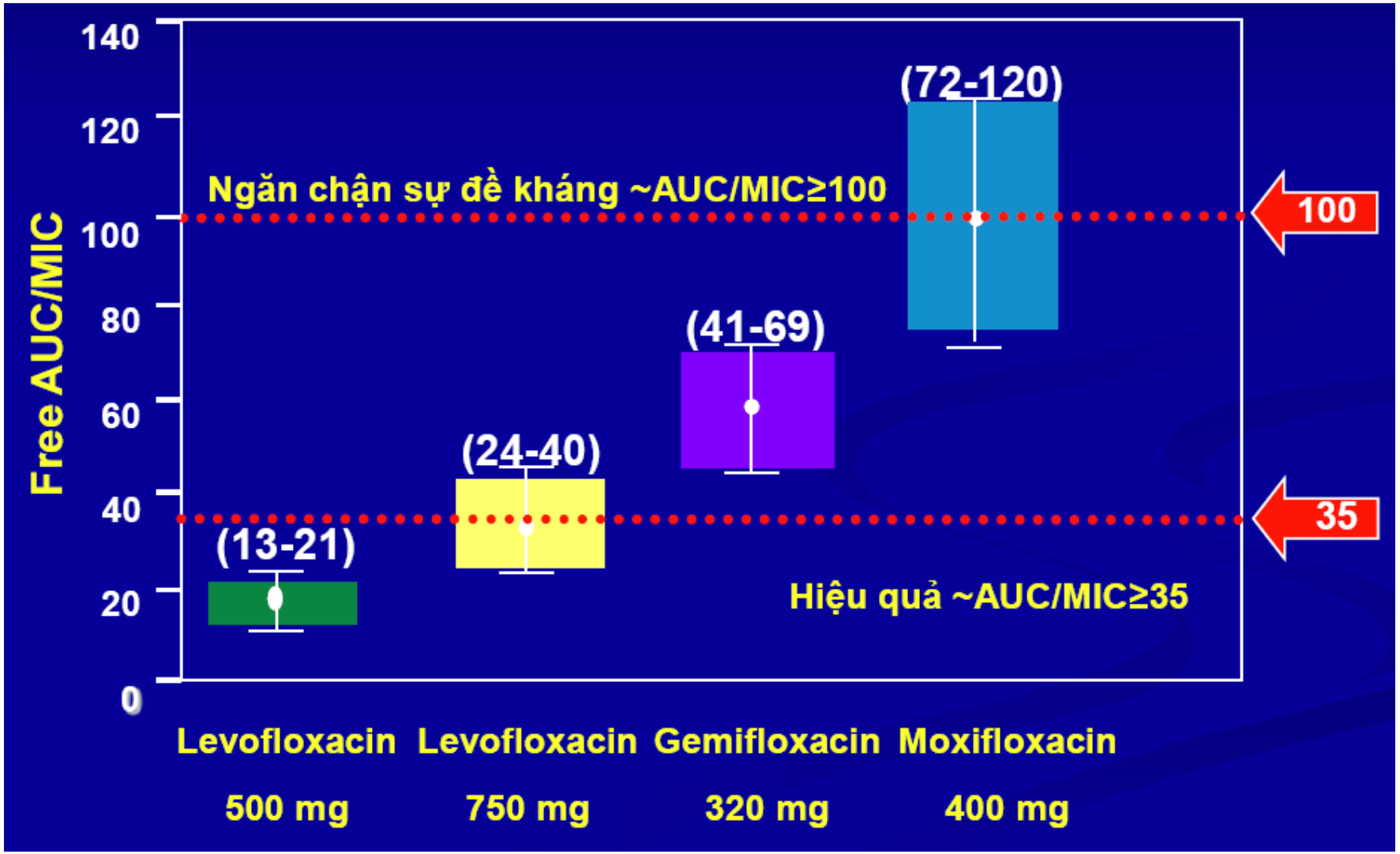
PK/PD ÁP DỤNG LỰA CHỌN FLUOROQUINOLON: PHÂN BỐ CỦA KHÁNG SINH VÀO VỊ TRÍ NHIỄM TRÙNG



MPC, mutant prevention concentration

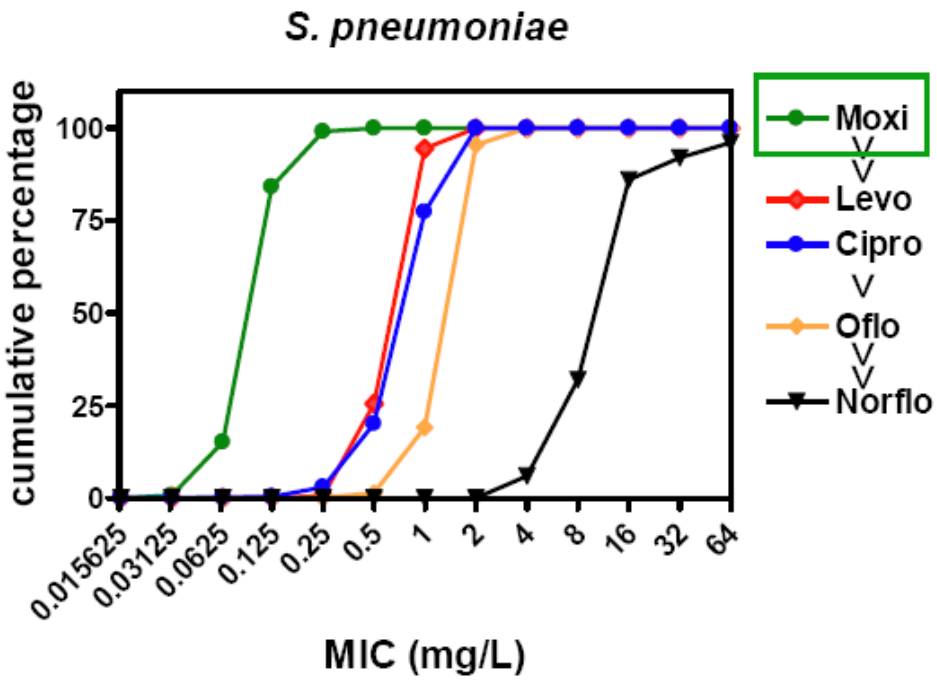
Capitano *et al. CHEST* 2004; 125: 965–73

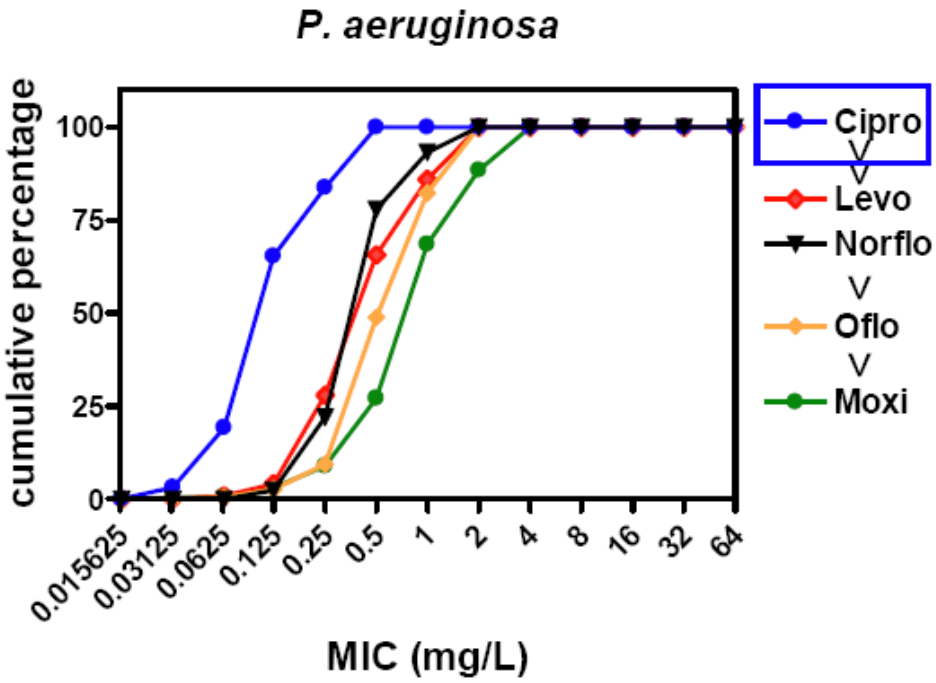
So sánh PK/PD của FQ để tối ưu hóa hiệu quả và chống *S. pneumoniae* kháng thuốc



Moran, J. Emerg. Med.(2006) 30: 377–87

PK/PD ÁP DỤNG LỰA CHỌN KHÁNG SINH QUINOLON

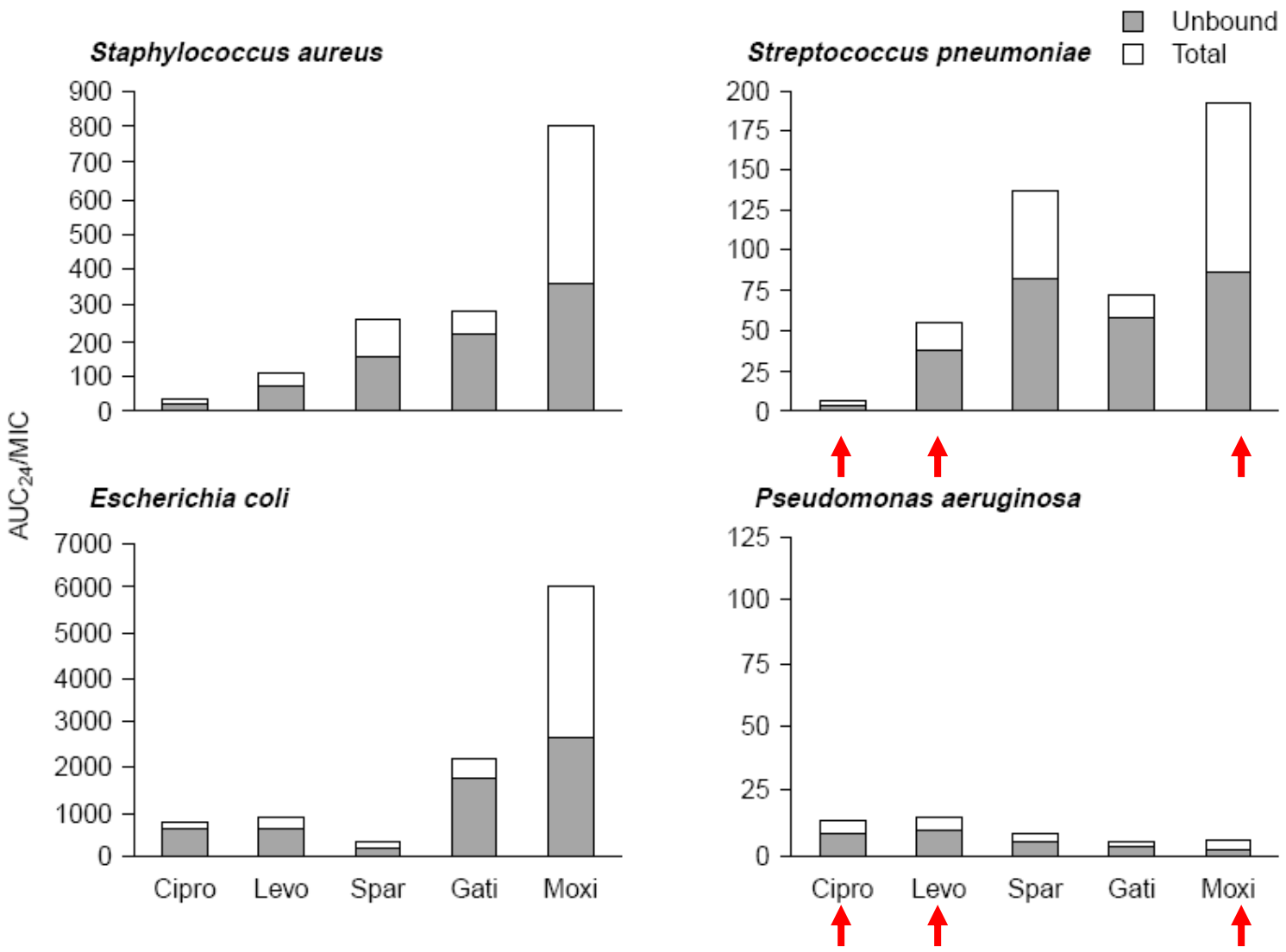




Cumulative MIC distributions for wild-type populations of *S. pneumoniae or P. aeruginosa*
(redrawn from data of EUCAST)
[European Committee on Antimicrobial Susceptibility Testing]

PK/PD ÁP DỤNG LỰA CHỌN KHÁNG SINH QUINOLON

Sự khác biệt PK/PD

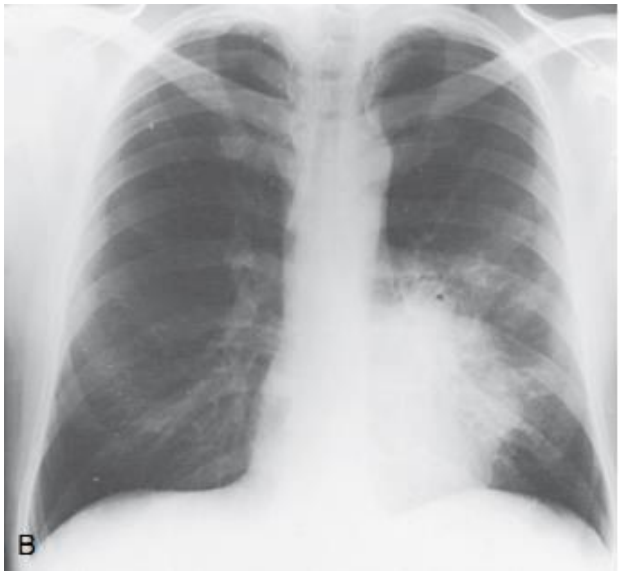


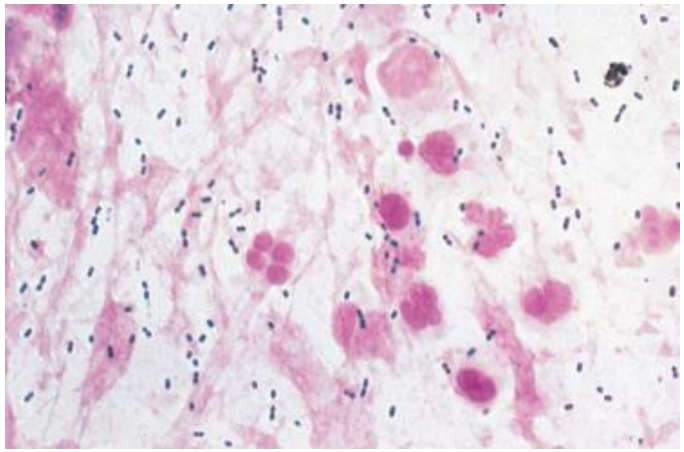
Nguồn: Clin. Pharmacokinet. 2001; 40: 169-187

ÁP DỤNG PK/PD TRONG ĐIỀU TRỊ VIÊM PHỔI

Viêm phổi cộng đồng và viêm phổi bệnh viện: căn nguyên vi sinh

- CAP: tùy thuộc yếu tố nguy cơ, bệnh nhân nội trú hay ngoại trú: *S. pneumoniae* (có cả DRSP), các căn nguyên nhiễm trùng hô hấp khác (kể cả vi khuẩn không điển hình), *P. aeruginosa* (viêm phổi nặng) và vi khuẩn kỵ khí (viêm phổi hít)
- HAP: vi khuẩn Gram âm sinh lactose (*K. pneumoniae*), không sinh lactose (*P. aeruginosa*, *A. baumanii*), Gram dương (*S. aureus*)





ÁP DỤNG PK/PD TRONG ĐIỀU TRỊ VIÊM PHỔI

Điều trị CAP theo một số khuyến cáo

	BTS guidelines [24]	ATS/IDSA guidelines [25]	ERS/ESCMID guidelines [26]
Low severity patients*	Use CURB65 score with clinical judgement Treat with oral amoxicillin or (doxycycline or clarithromycin if hypersensitive).	Use CURB65 or PSI score to guide Outpatient treatment Stratify by risk for drug resistant *S. pneumoniae* Low risk: Treat with macrolide or doxycycline High risk: Treat with respiratory fluoroquinolone or b-lactam+macrolide	Use CRB65 to guide Outpatient treatment Treat with one of: aminopenicillin ± macrolide Aminopenicillin/b-lactamase inhibitor ± macrolide Non-antipseudomonal cephalosporin Cefotaxime or ceftriaxone ± macrolide Levofloxacin Moxifloxacin Penicillin g ± macrolide
Moderate/high severity patients*	CURB65 score 3 or more consider ICU Treat with β-lactam plus macrolide iv	Consider ICU for sepsis or >2 minor severity criteria Increased Comorbidities or prior antimicrobials (within 3 months) treat with respiratory fluoroquinolone or beta lactam plus macrolide iv	Consider ICU for respiratory failure or sepsis or >2 minor severity criteria Stratify by risk for *Pseudomonas aeruginosa* Non-antipseudomonal treat with cephalosporin III + macrolide Or Moxifloxacin or levofloxacin ± non-antipseudomonal cephalosporin III

Liều quinolon hô hấp

- Levofloxacin 750 mg IV q24h
- Moxifloxacin 400 mg IV q24h
- Chuyển IV→ PO khi điều kiện lâm sàng cho phép

BTS guidelines. *Thorax* 2009; 64 (suppl 3): iii 1-55
ATS/IDSA guidelines. *Clin Infect. Dis.* 2007; 44 (Suppl 2): S27-72.
ERS/ESCMID guidelines. *Clin. Infect. Microbiol.* 2011; 17 (Suppl 6): E1-59

ÁP DỤNG PK/PD TRONG ĐIỀU TRỊ VIÊM PHỔI

Khuyến cáo lựa chọn/liều dùng kháng sinh kinh nghiệm điều trị HAP

Phân loại	Nguyên nhân chính	Kháng sinh ưu tiên
VPBV sớm (không có nguy cơ nhiễm vi khuẩn kháng thuốc)	*S. pneumoniae*, *Streptococcus* spp., MSSA, *H.influenzae*, *E.coli*, *Klebsiella* spp., *Enterobacter*, *Proteus* spp. và *Serratia* spp.	Cephalosporin, thế hệ III: Ceftriaxon 1-2 g mỗi 24h TM hoặc Cefotaxim 1-2 g mỗi 8h, TM **Hoặc** Cephalosporin, thế hệ IV: Cefepim 1-2 g mỗi 12h, TM **Hoặc** Beta-lactam-chất ức chế beta-lactamase (Piperacilin-tazobactam 4,5 g mỗi 8h TM) **Hoặc** Fluoroquinolon: Levofloxacin 750 mg mỗi 24h TM hoặc Moxifloxacin 400 mg mỗi 24h TM

Bộ Y tế, Hướng dẫn điều trị kháng sinh, 2015.

ATS guidelines 2005; AJRCCM 171: 388-416

ÁP DỤNG PK/PD TRONG ĐIỀU TRỊ VIÊM PHỔI

Khuyến cáo lựa chọn/liều dùng kháng sinh kinh nghiệm điều trị HAP

VPBV muộn (có nguy cơ nhiễm VK	*S. pneumoniae,* *Streptococcus* spp., MSSA,	Cephalosporin, thế hệ III: Ceftriaxon 1-2 g mỗi 24h TM hoặc Cefotaxim 1-2 g mỗi 8h TM
đa kháng) mức độ nhẹ và vừa	*H. influenzae,* *E.coli* *Klebsiella* spp., *Enterobacter* *Proteus* spp. và *Serratia* spp. *P. aeruginosa* *Acinetobacter* spp.	**Hoặc** Cephalosporin, thế hệ IV: Cefepim 1-2 g mỗi 8-12h, TM **Hoặc** Beta-lactam-chất ức chế beta-lactamase (Piperacilin-tazobactam 4,5 g mỗi 6h, TM) **Hoặc** Carbapenem: Imipenem 500mg mỗi 8h truyền TM hoặc meropenem 500mg mỗi 8h, đường TM **Hoặc** Fluoroquinolon: Levofloxacin 750 mg mỗi 24h, TM hoặc Moxifloxacin 400 mg mỗi 24h, TM
	Có thể gặp MRSA	**Phối hợp hoặc không:** Vancomycin 1 g mỗi 12h, TM hoặc linezolid 600 mg mỗi 12h, TM (nếu có hoặc nghi ngờ MRSA)

Bộ Y tế, Hướng dẫn điều trị kháng sinh, 2015.

ATS guidelines 2005; AJRCCM 171: 388-416

ÁP DỤNG PK/PD TRONG ĐIỀU TRỊ VIÊM PHỔI

Khuyến cáo lựa chọn/liều dùng kháng sinh kinh nghiệm điều trị HAP

VPBV muộn nặng phải điều trị tại ICU	*S. pneumoniae,* *Streptococcus* spp. MRSA *H. influenzae,* *Escherichia coli,* *Klebsiella* spp. *Enterobacter* *Proteus* spp. và *Serratia* spp. *P. aeruginosa* *Acinetobacter* spp. *Legionella* spp.	Cephalosporin kháng *Pseudomonas* Ceftazidim 2g mỗi 8h hoặc cefepim 1-2 g mỗi 8-12h, TM **Hoặc** Beta-lactam-chất ức chế beta-lactamase (Piperacilin-tazobactam 4,5 g mỗi 6h, TM) **Hoặc** Carbapenem: Imipenem 500mg – 1g mỗi 6h, truyền TM hoặc meropenem 1g mỗi 8h, đường TM **Phối hợp với:** Fluoroquinolon: Ciprofloxacin 400 mg mỗi 8h TM hoặc Levofloxacin 750 mg mỗi 24h, TM Hoặc Aminoglycosid: Gentamicin hoặc tobramycin 5-7 mg/kg mỗi 24h, TM hoặc amikacin 15-20 mg/kg mỗi 24h, TM **Phối hợp hoặc không:** Vancomycin 1g mỗi 12h, TM hoặc linezolid 600 mg mỗi 12h, TM (nếu có hoặc nghi ngờ MRSA)

Bộ Y tế, Hướng dẫn điều trị kháng sinh, 2015.

ATS guidelines 2005; AJRCCM 171: 388-416

ỨNG DỤNG PK/PD TRONG XÂY DỰNG HƯỚNG DẪN ĐIỀU TRỊ: VÍ DỤ VIÊM MŨI XOANG

SUPPLEMENT TO
Otolaryngology–Head and Neck Surgery
JANUARY 2004 VOLUME 130 NUMBER 1

Antimicrobial treatment guidelines for acute bacterial rhinosinusitis

Executive Summary

SINUS AND ALLERGY HEALTH PARTNERSHIP*

Treatment guidelines developed by the Sinus and Allergy Health Partnership for acute bacterial rhinosinusitis (ABRS) were originally published in 2000. These guidelines were designed to: (1) educate clinicians and patients (or patients' families) about the differences between viral and bacterial rhinosinusitis; (2) reduce the use of antibiotics for nonbacterial nasal/sinus disease; (3) provide recommendations for the diagnosis and optimal treatment of ABRS; (4) promote the use of appropriate antibiotic therapy when bacterial infection is likely; and (5) describe the current understanding of pharmacokinetic and pharmacodynamics and how they relate to the effectiveness of antimicrobial therapy. The original guidelines are updated here to include the most recent information on management principles, antimicrobial susceptibility patterns, and therapeutic options.

Reprint requests: Sinus and Allergy Health Partnership, 1990 M Street NW, Suite 680, Washington, DC 20036.

*The Sinus and Allergy Health Partnership is a not-for-profit organization created through the joint efforts of the American Academy of Otolaryngic Allergy, the American Academy of Otolaryngology–Head and Neck Surgery, and the American Rhinologic Society. Development of this paper was funded by the Sinus and Allergy Health Partnership.

Some antibiotics discussed in this document currently are not approved by the US Food and Drug Administration for the treatment of maxillary sinusitis in adults or children, while the value of others approved when antimicrobial resistance rates were very low is now very limited.

0194-5998/$30.00

doi:10.1016/j.otohns.2003.12.003

Burden of Disease

An estimated 20 million cases of ABRS occur annually in the United States. According to National Ambulatory Medical Care Survey (NAMCS) data, sinusitis is the fifth most common diagnosis for which an antibiotic is prescribed. Sinusitis accounted for 9% and 21% of all pediatric and adult antibiotic prescriptions, respectively, written in 2002. The primary diagnosis of sinusitis results in expenditures of approximately $3.5 billion per year in the United States.

Definition and Diagnosis of ABRS

ABRS is most often preceded by a viral upper respiratory tract infection (URI). Allergy, trauma, dental infection, or other factors that lead to inflammation of the nose and paranasal sinuses may also predispose individuals to developing ABRS.

Patients with a "common cold" (viral URI) usually report some combination of the following symptoms: sneezing, rhinorrhea, nasal congestion, hyposmia/anosmia, facial pressure, postnasal drip, sore throat, cough, ear fullness, fever, and myalgia. A change in the color or the characteristic of the nasal discharge is not a specific sign of a bacterial infection. Bacterial superinfection may occur at any time during the course of a viral URI. The risk that bacterial superinfection has occurred is greater if the illness is still present after 10 days.

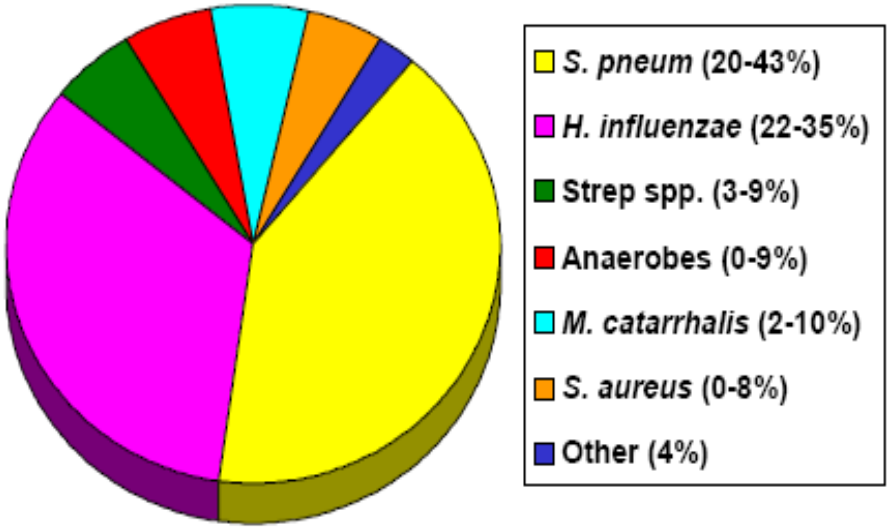
Sử dụng PK/PD để xây dựng hướng dẫn điều trị viêm mũi xoang nhiễm khuẩn

Mô hình "kết cuộc điều trị" được xây dựng dựa trên:

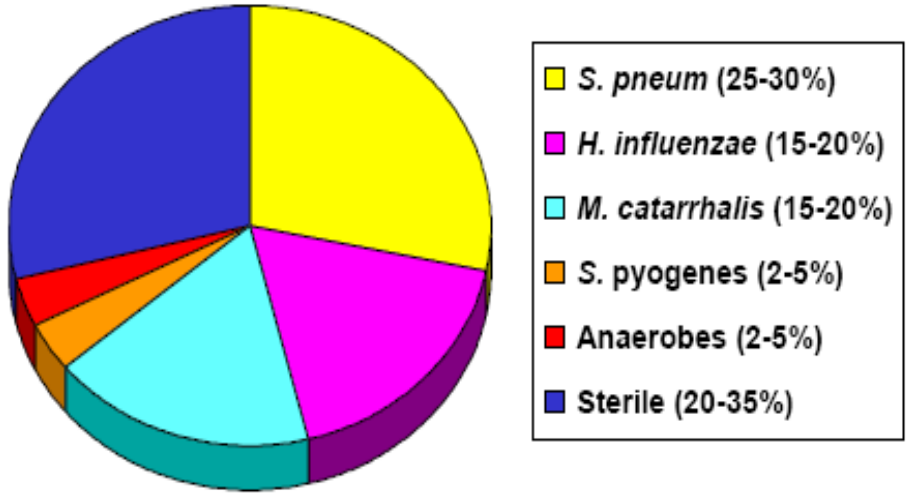
- Tần suất vi khuẩn gây bệnh chính trong viêm mũi xoang cấp
- Tỷ lệ tự "thoái lui" với mỗi loại vi khuẩn gây bệnh
- Khả năng sạch khuẩn với mỗi loại vi khuẩn gây bệnh dựa trên độ nhạy cảm tại giá trị điểm gãy xác định theo PK/PD

Tần suất vi khuẩn gây bệnh trong viêm mũi xoang cấp

Microbiology of Acute Bacterial Rhinosinusitis (Adults)



Microbiology of Acute Bacterial Rhinosinusitis (Children)



Sinus and Allergy Health Partnership. *Otolaryngol Head Neck Surg* 2000; **123**(supp 1 part 2):S1–S32

Breakpoint xác định theo PK/PD của các kháng sinh uống sử dụng trong điều trị nhiễm khuẩn hô hấp

	PK/PD breakpoint (µg/ml)
	ALL ORGANISMS
Amoxicillin	2
Amox/clav	2
Cefuroxime axetil	1
Cefprozil	1
Cefixime	0.5
Cefaclor	0.5
Loracarbef	0.5
Azithromycin	0.12
Clarithromycin	0.25

Based on M100-S11, National Committee for Clinical Laboratory Standards, 2001; Sinus and Allergy Health Partnership. *Otolaryngol Head Neck Surg* 2000; **123**(supp 1 part 2):S1–S32.

So sánh breakpoint xác định theo PK/PD và breakpoint của CLSI (NCCLS cũ)

	NCCLS		PK/PD
	S. pneumoniae	*H. influenzae*	ALL ORGANISMS
Amoxicillin	2	4	2
Amox/clav	2	4	2
Cefuroxime axetil	1	4	1
Cefprozil	2	8	1
Cefixime	–	1	0.5
Cefaclor	1	8	0.5
Loracarbef	2	8	0.5
Azithromycin	0.5	4	0.12
Clarithromycin	0.25	8	0.25

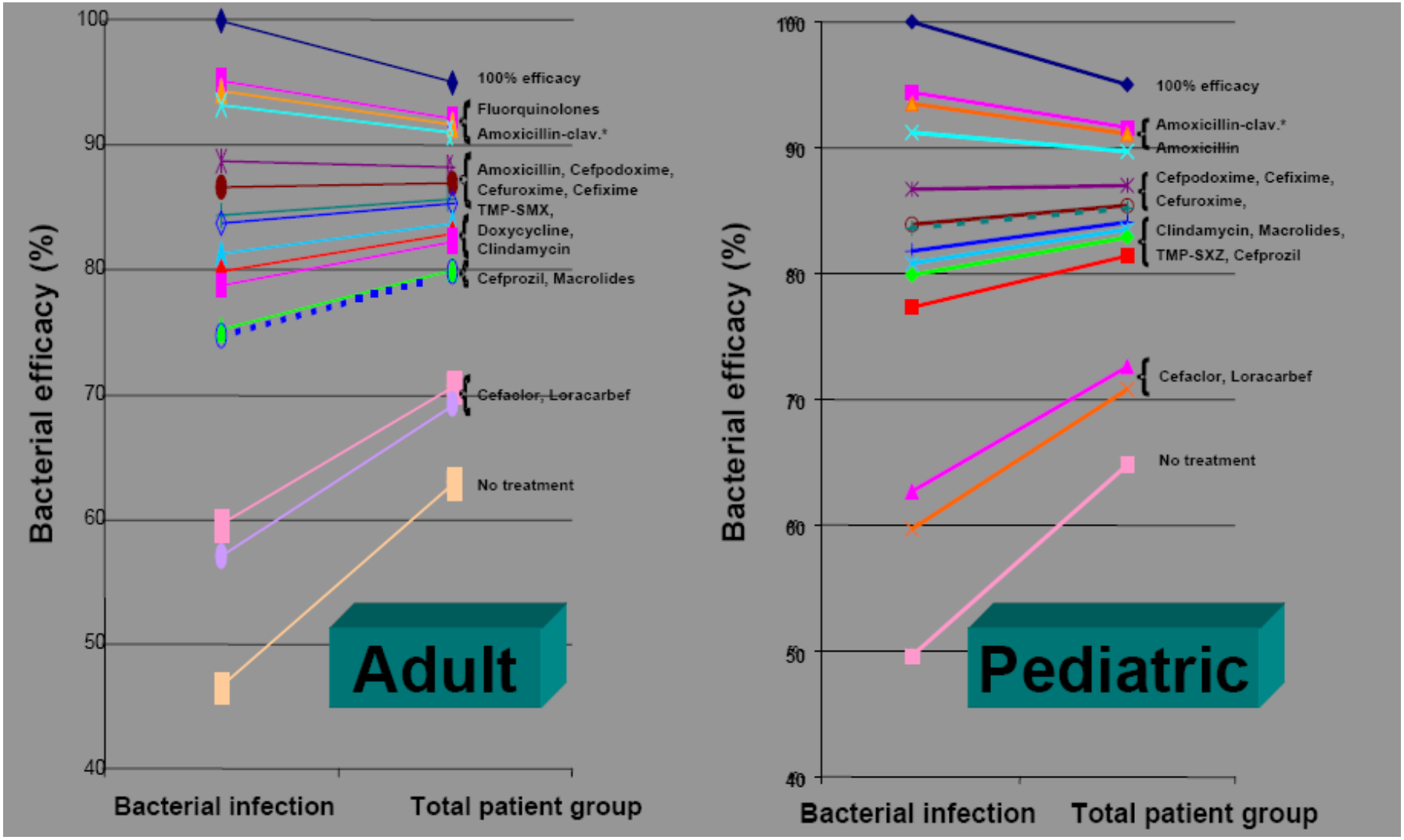
Based on M100-S11, National Committee for Clinical Laboratory Standards, 2001; Sinus and Allergy Health Partnership. *Otolaryngol Head Neck Surg* 2000; **123**(supp 1 part 2):S1–S32.

Độ nhạy cảm của các chủng VK phân lập tại Hoa kỳ tại giá trị breakpoint xác định theo PK/PD

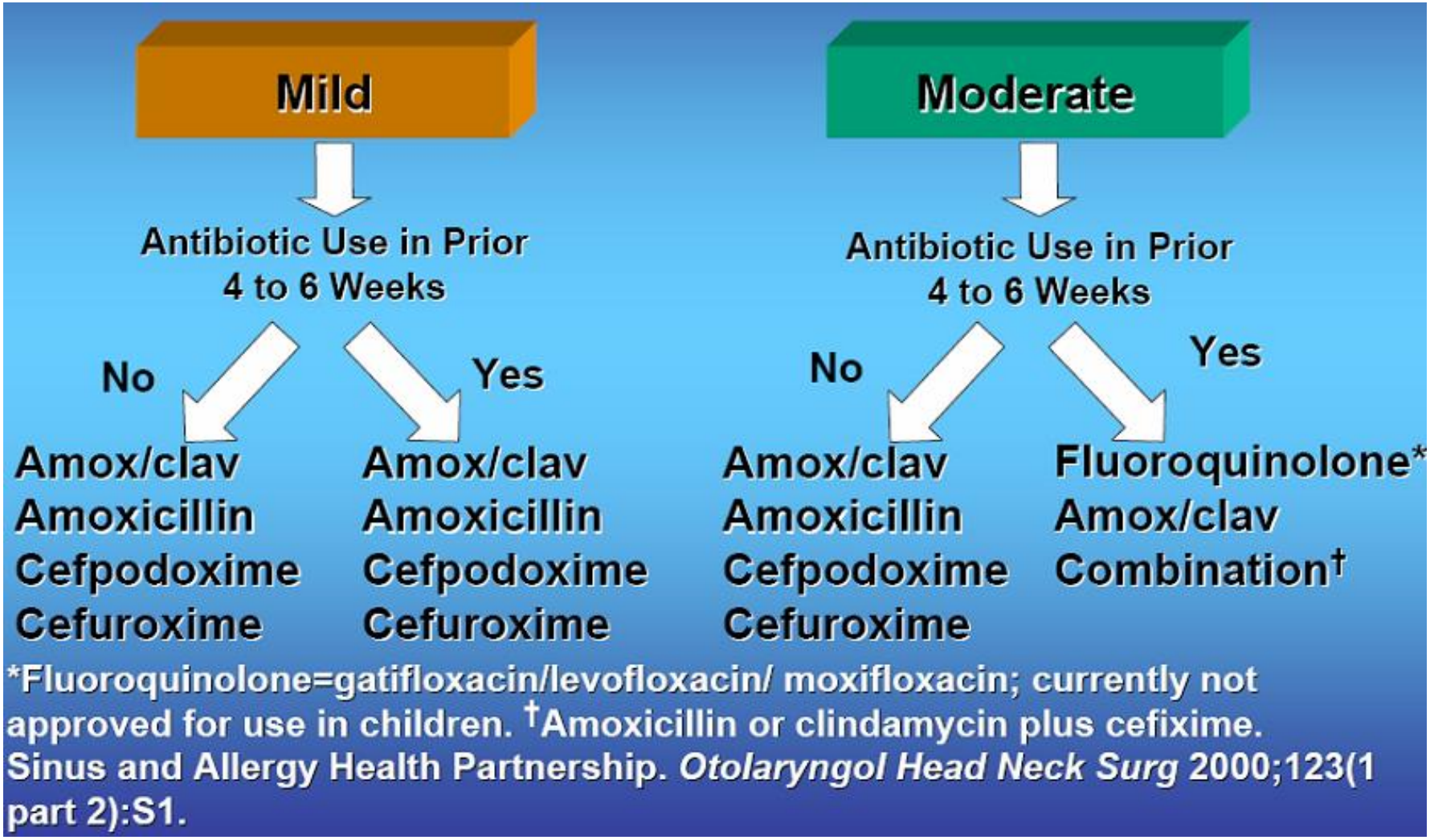
	Percentage of strains susceptible		
Agent	*S. pneumoniae*	*H. influenzae*	*M. catarrhalis*
Amox/clav	90	97	100
Amoxicillin	90	61	14
Cefaclor	27	2	5
Cefixime	57	99	100
Cefpodoxime	63	99	64
Cefprozil	64	18	6
Cefuroxime	64	79	37
Cefdinir‡	61	97	100
Azithromycin	67	0	100
Clindamycin*	89	NA	NA
Doxycycline	76	20	96
Levofloxacin	99.8	100	99
TMP/SMX*	57	75	9

Based on M100-S11, National Committee for Clinical Laboratory Standards, 2001; Sinus and Allergy Health Partnership. *Otolaryngol Head Neck Surg* 2000; **123**(supp 1 part 2):S1–S32. ‡Jacobs M. (unpublished)

Mô hình "kết cuộc điều trị" trong viêm mũi xoang



Khuyến cáo điều trị kháng sinh trong viêm mũi xoang cấp tính của Hội Phẫu thuật TMH, Đầu-Mặt-Cổ Hoa kỳ

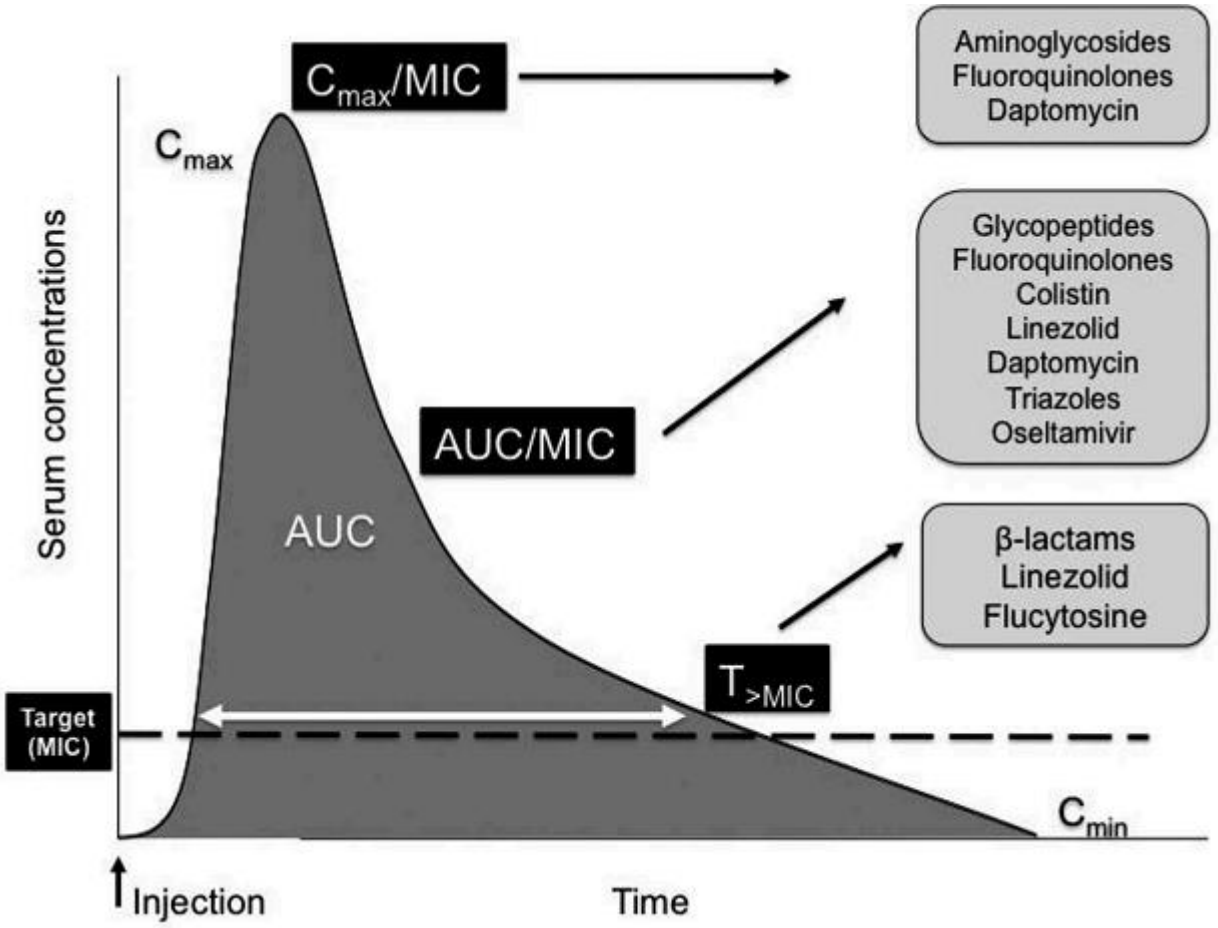


*Fluoroquinolone=gatifloxacin/levofloxacin/ moxifloxacin; currently not approved for use in children. †Amoxicillin or clindamycin plus cefixime.

Sinus and Allergy Health Partnership. *Otolaryngol Head Neck Surg* 2000;123(1 part 2):S1.

ỨNG DỤNG PK/PD TRONG XÁC ĐỊNH NỒNG ĐỘ ĐÍCH VÀ LỰA CHỌN CHẾ ĐỘ LIỀU CHO BỆNH NHÂN NẶNG

"HIT HARD & HIT FAST": tối ưu hóa sử dụng kháng sinh dựa trên PK/PD

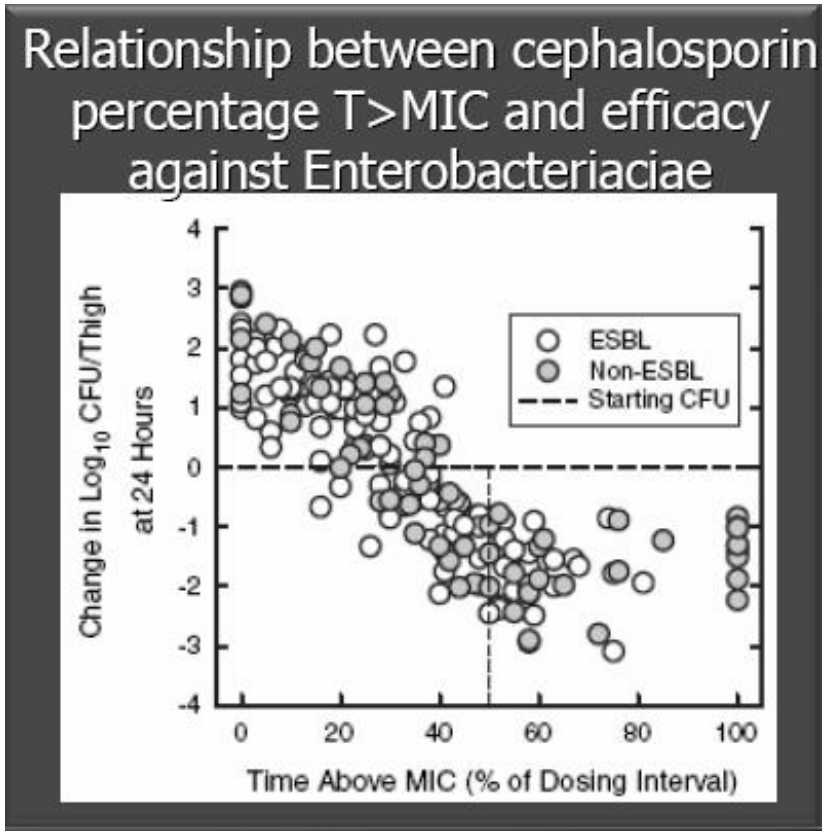


Jager NG et al. Expert Rev. Clin. Pharmacol. 2016; 9: 961-979

Điều trị các chủng vi khuẩn giảm nhạy cảm

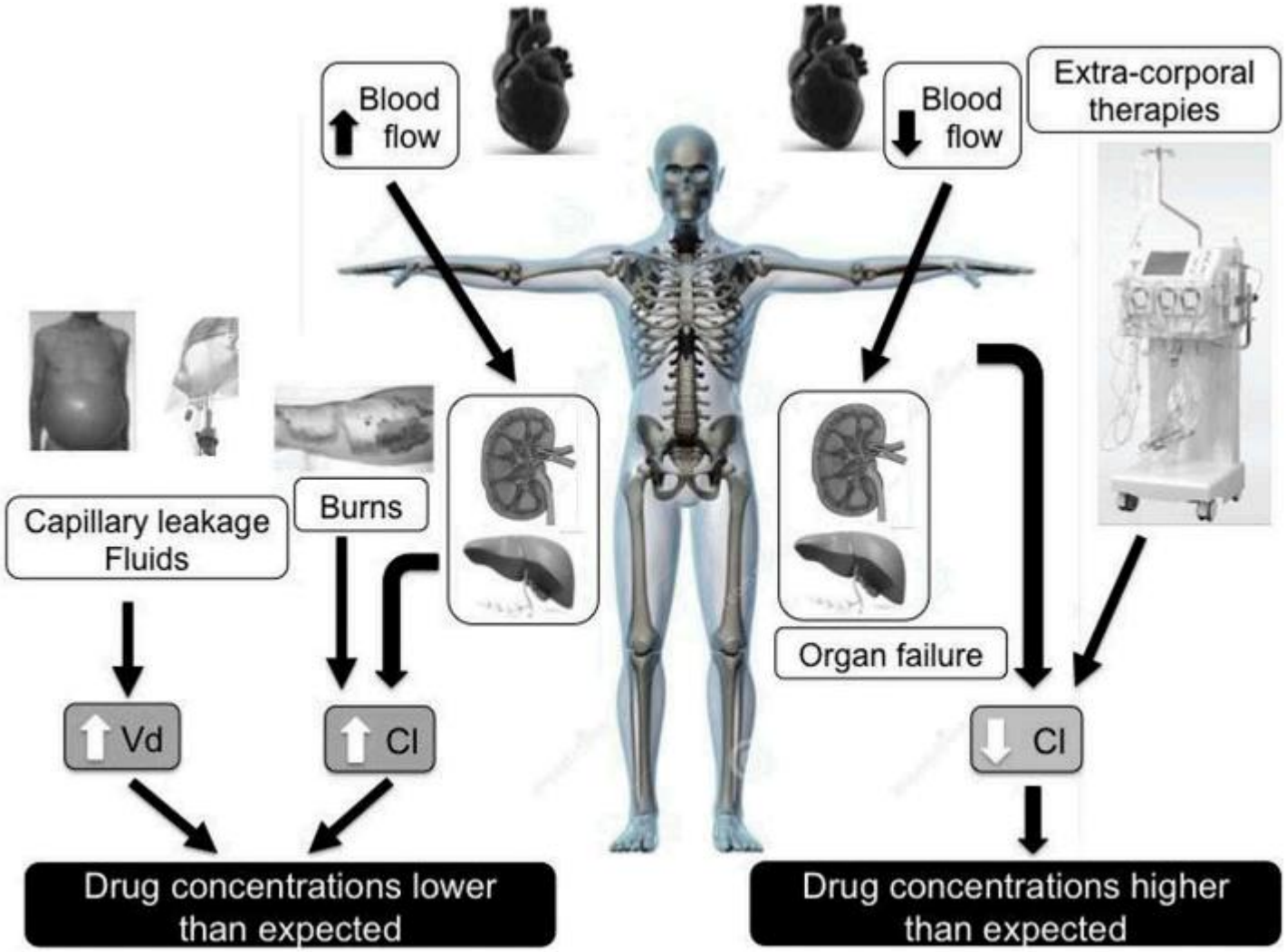
Kháng sinh β-lactam: chỉ số PK/PD dự đoán hiệu quả nhiễm trùng

- Non-ESBL = vi khuẩn sinh ESBL: MIC cao hơn (thách thức)



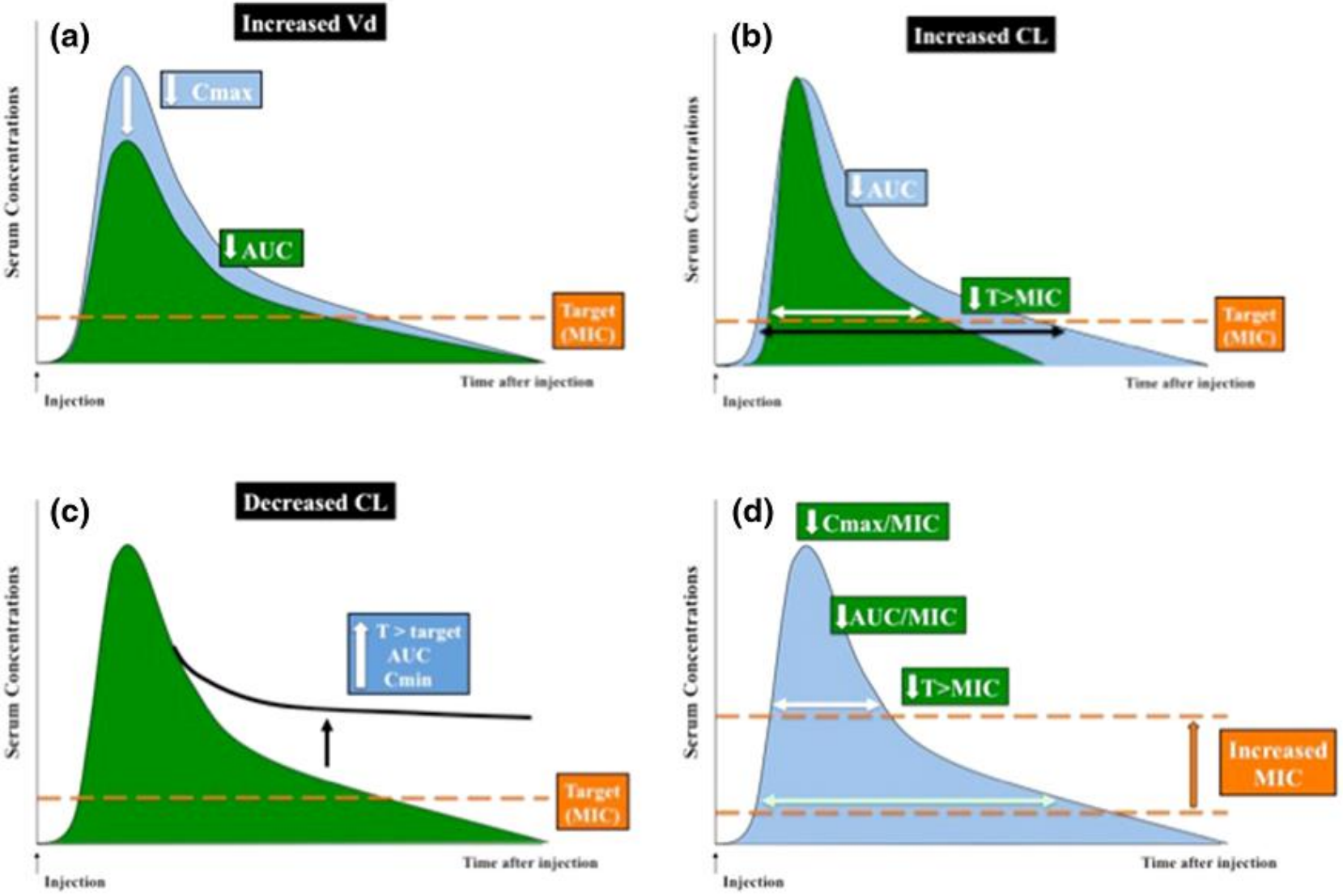
Andes D, Craig W, CMI 2005; 11 (s6): 10

Thay đổi sinh lý bệnh liên quan đến Dược động học (PK) của kháng sinh ở bệnh nhân nặng



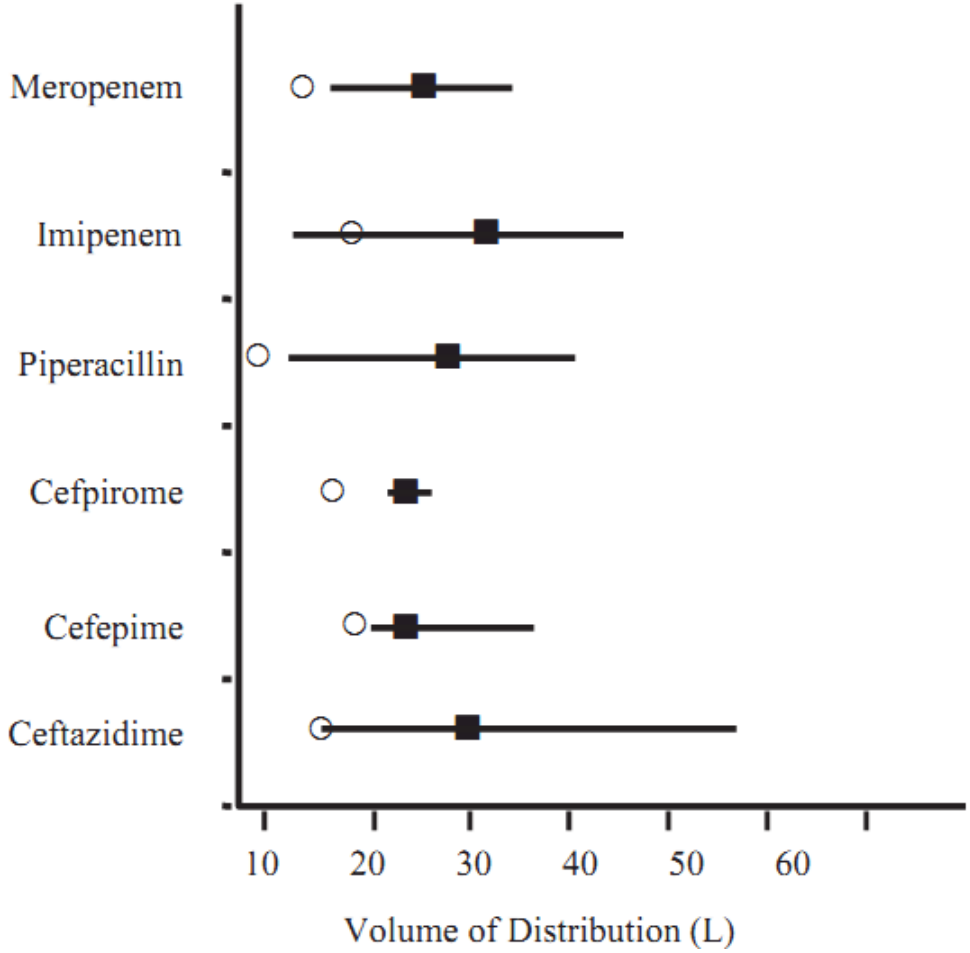
Pea F et al. Clin. Pharmacokinet. 2005; 44: 1009-1034. Blanchet B et al. Clin. Pharmacokinet. 2008: 47: 635-654

Thay đổi sinh lý bệnh liên quan đến Dược động học (PK) của kháng sinh ở bệnh nhân nặng



Roberts JA et al. Intens. Care Med. 2016

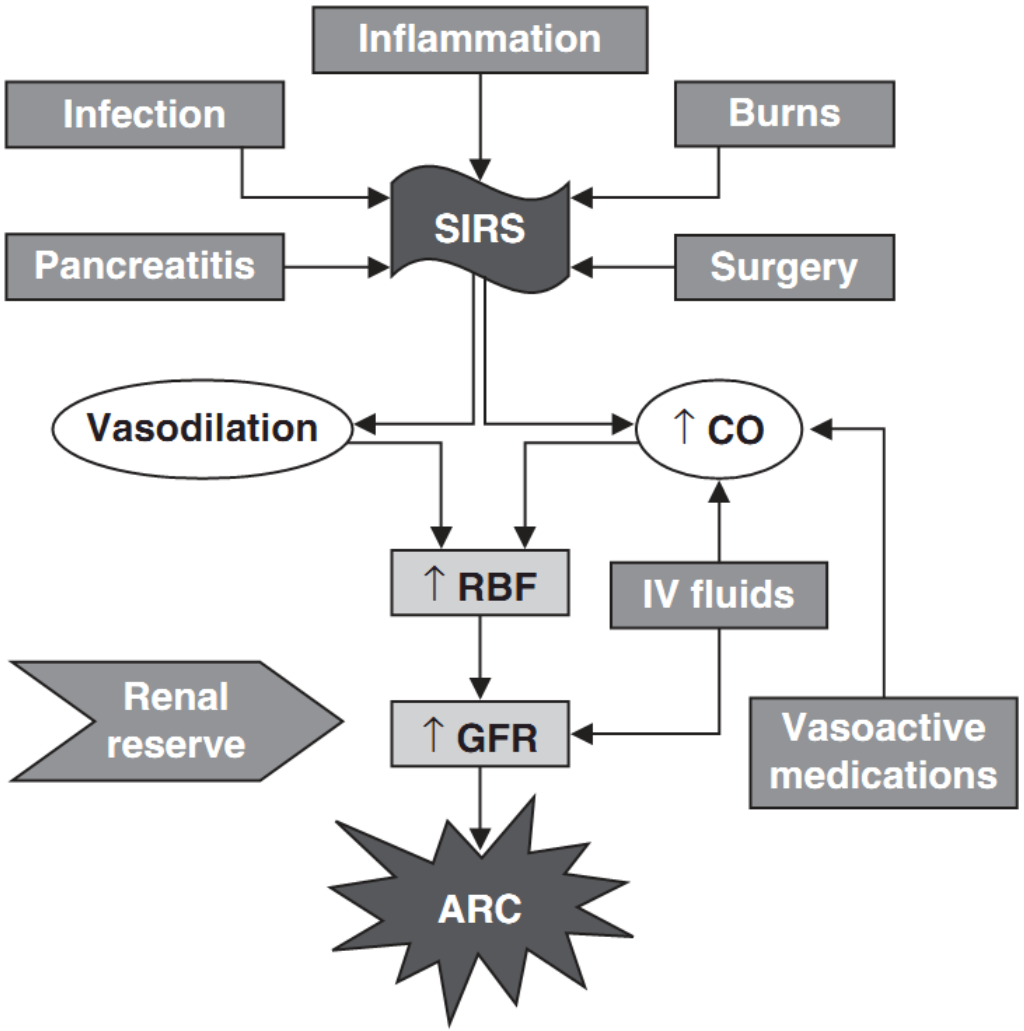
THAY ĐỔI THỂ TÍCH PHÂN BỐ Ở BỆNH NHÂN NẶNG VÀ CHẾ ĐỘ LIỀU KHÁNG SINH



Thay đổi thể tich phân bố của kháng sinh beta-lactam ở bệnh nhân ICU (vuông) so với người tình nguyện khỏe mạnh (chấm tròn)

Goncalve-Pereira J, Povoa P. Crit. Care 2011; 15: R206

TĂNG THANH THẢI THẬN Ở BỆNH NHÂN NẶNG VÀ CHẾ ĐỘ LIỀU KHÁNG SINH



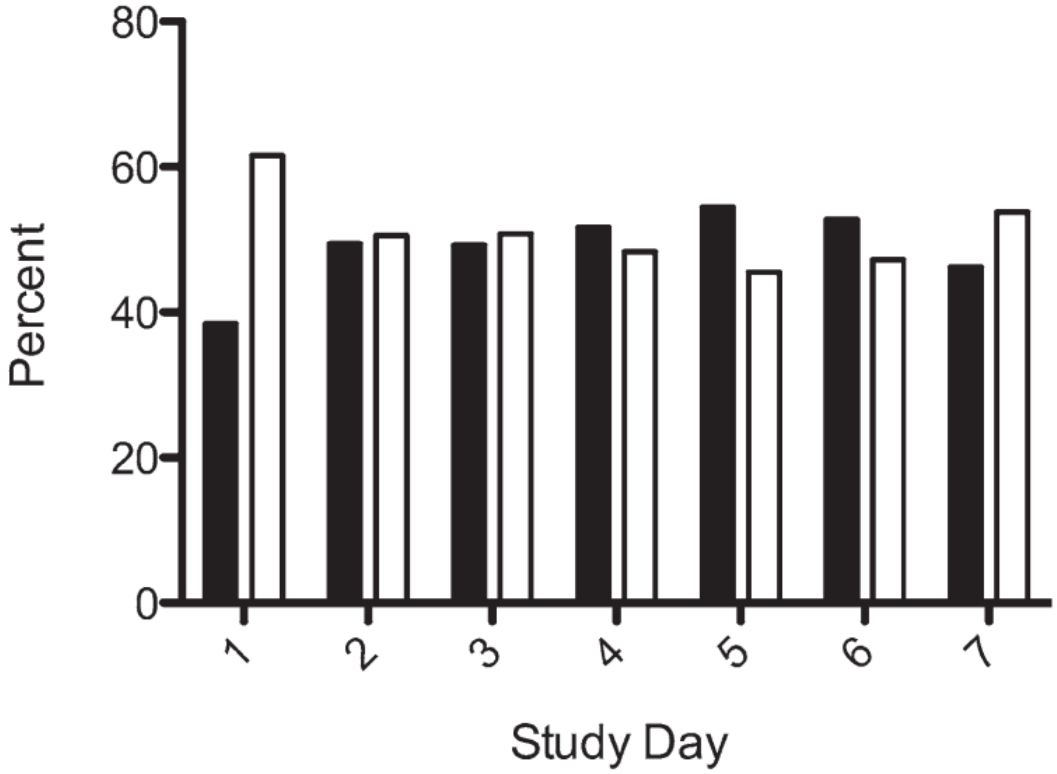
Cơ chế của ARC ở bệnh nhân nặng

CO = cung lượng tim; GFR = tốc độ lọc cầu thận; RBF = lưu lượng máu thận

- Tăng thanh thải thận (ARC): tăng thải trừ các chất hòa tan (bao gồm thuốc) qua thận
- Liên quan đến SIRS, sử dụng vận mạch, truyền dịch thay đổi chức năng ống thận, huy động dự trữ thận
- Định nghĩa: GFR > 160 ml/phút ở nam và > 150 ml/phút ở nữ

Udy AA et al. Clin. Pharmacokinet. 2010; 49: 1-16; Nat. Rev. Nephrol. 2011; 7: 539-543

TĂNG THANH THẢI THẬN Ở BỆNH NHÂN NẶNG VÀ CHẾ ĐỘ LIỀU KHÁNG SINH



ARC =	108	114	87	74	67	56	43
n =	281	231	177	143	123	106	93

Box 1 | Risk factors for ARC

Patient-related factors

- Younger age (<60 years)
- Pregnancy

Disease-related factors

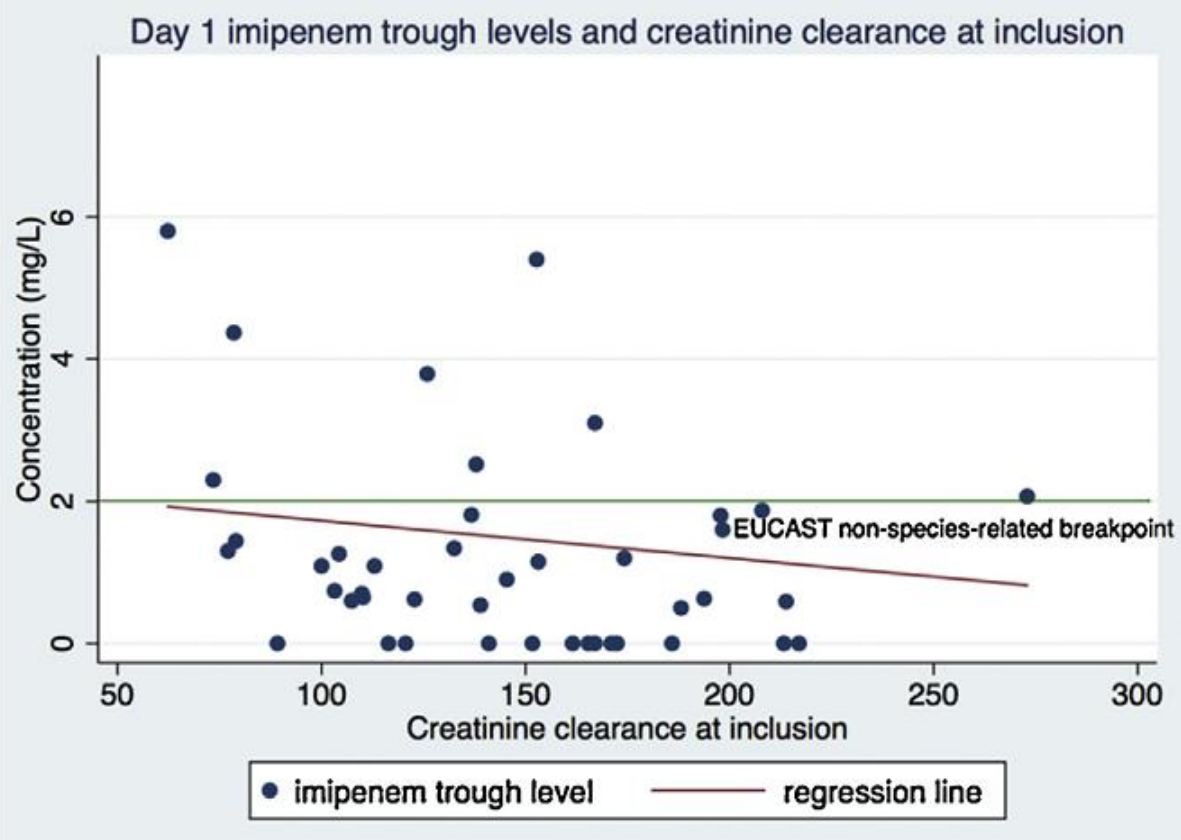
- Sepsis
- Trauma
- Surgery or neurosurgery
- Febrile neutropenia owing to hematological malignancy
- Burns injury
- Cystic fibrosis

Abbreviation: ARC, augmented renal clearance.

Tần suất ARC (solid bars) ở bệnh nhân nặng trong 7 ngày đầu tiên tại ICU: cohort trên 281 BN

Udy AA et al. Crit. Care Med 2014; 42: 520-527; Nat. Rev. Nephrol. 2011; 7: 539-543

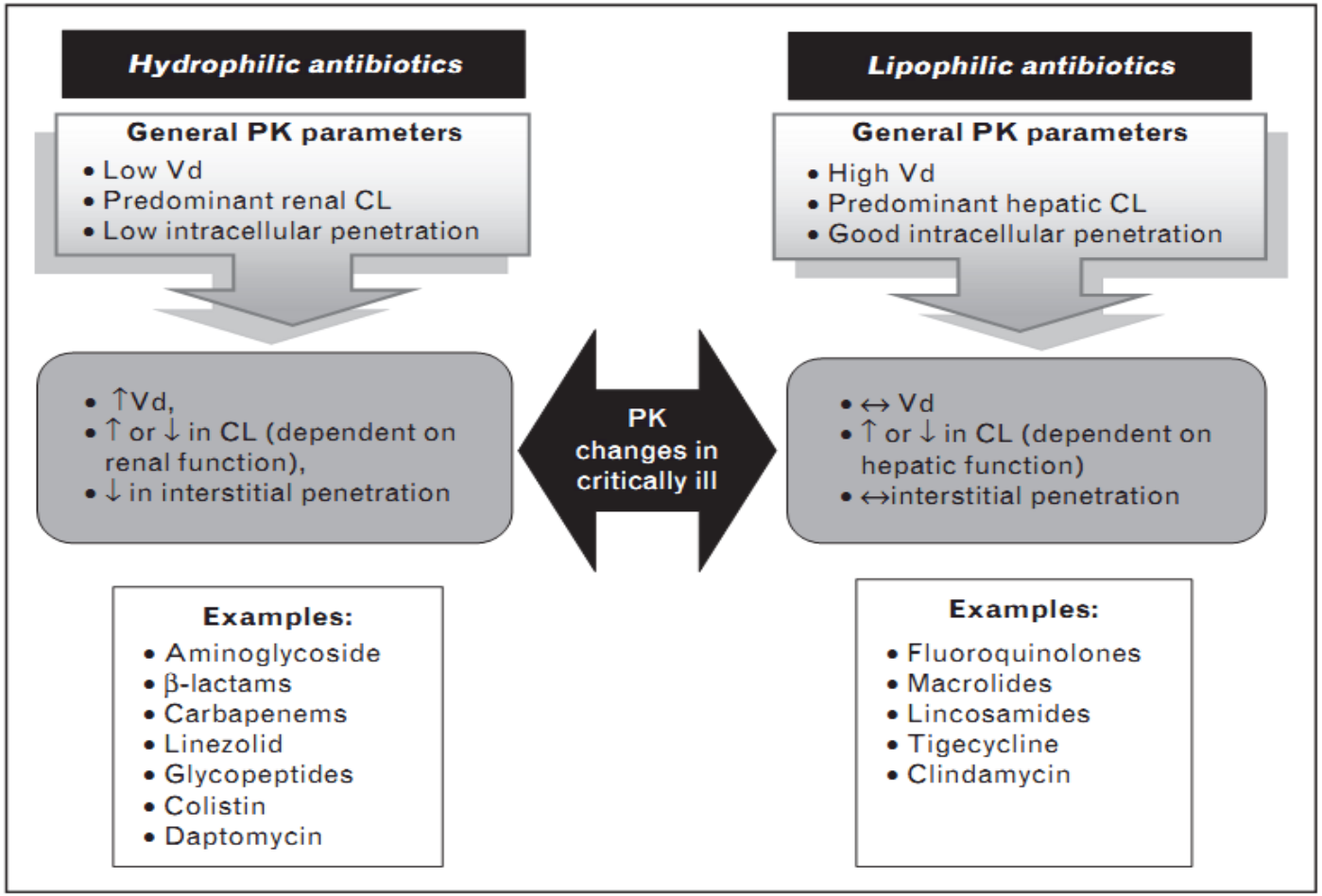
ARC Ở BỆNH NHÂN NẶNG ẢNH HƯỞNG ĐẾN PK/PD CỦA β-LACTAM



64% BN ICU có ARC trong ngày 5 ngày đầu dùng imipenem, tăng nguy cơ nồng độ đáy quá thấp không phát hiện được (OR = 3.3; CI95% = 1.11-9.94): kết quả từ cohort trên 100 BN ICU

Huttner A et al. Int. J. Antimicrob. Agents 2015; 45: 385-392

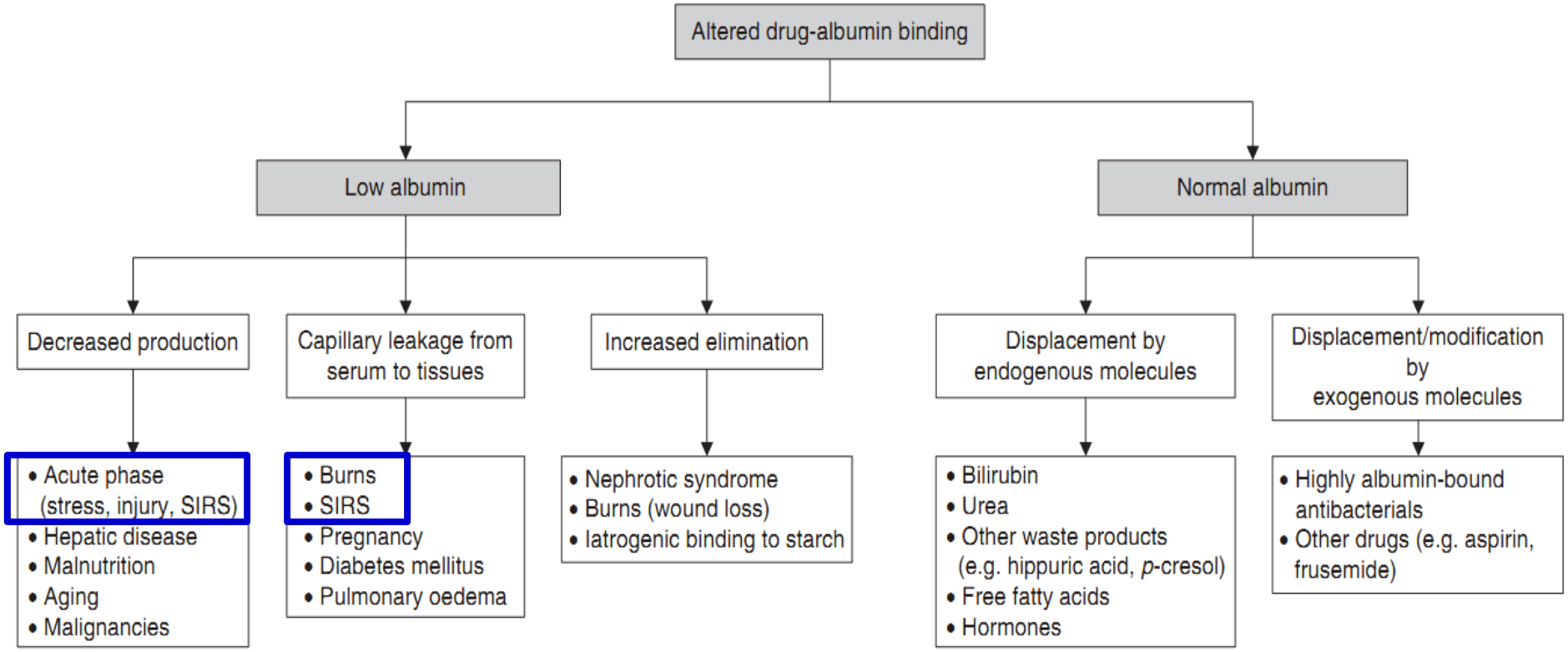
Thay đổi sinh lý bệnh liên quan đến PK/PD kháng sinh ở bệnh nhân nặng



- Kháng sinh chịu ảnh hưởng: thân nước (beta-lactam, vancomycin, aminosid, colistin)
- Vd nhỏ, thải trừ chủ yếu qua thận dưới dạng nguyên vẹn còn hoạt tính

Jamal JA et al. Curr. Opin. Crit. Care 2012; 18: 460-471.

GIẢM ALBUMIN MÁU Ở BỆNH NHÂN NẶNG VÀ CHẾ ĐỘ LIỀU KHÁNG SINH



Kháng sinh/kháng nấm chịu ảnh hưởng (liên kết nhiều với albumin huyết tương): oxacillin (93%), cefoperazon (90%), ceftriaxon (85%), daptomycin (90%), ertapenem (90%), teicoplanin (90-95%), tigecyclin (71-89%), itraconazol (99,8%), amphotericin B (90%), caspofungin (97%)

Ulldemolins M et al. Clin. Pharmacokinet. 2011; 50: 99-1110;

GIẢM ALBUMIN MÁU Ở BỆNH NHÂN NẶNG VÀ CHẾ ĐỘ LIỀU KHÁNG SINH (LIỀU NẠP + TĂNG SỐ LẦN ĐƯA THUỐC)

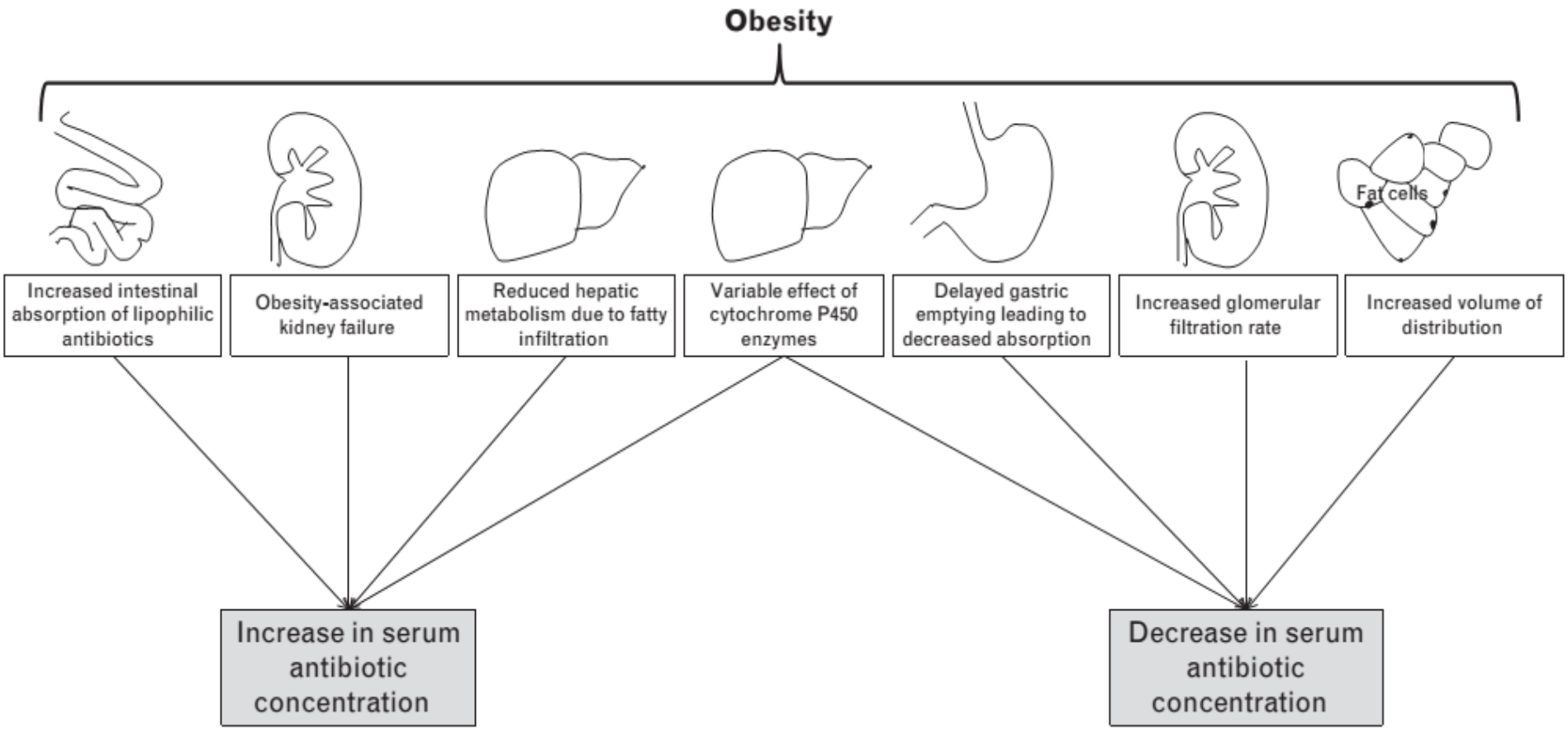
Antibacterial	Standard ICU dosing	Recommended LD in hypoalbuminaemia	Recommended MD in hypoalbuminaemia
β-lactams and carbapenems			
Aztreonam	1 g q8h	2 g q8h for 3 doses	Increase frequency of administration (e.g. 1 g q6h)
Ceftriaxone	1 g q12h	2 g for initial dose	Increase frequency of administration (e.g. 1 g q8h)
Cephalothin			
Flucloxacillin, dicloxacillin, cloxacillin	2 g q6h	2 g	Consider continuous infusion (e.g. 8–12 g q24h)
Ertapenem	1 g q24h	2 g for initial dose	Increase frequency of administration (e.g. 1 g q12h)
Glycopeptides			
Vancomycin	1 g q12h	20–30 mg/kg for initial dose	Increase dosing (e.g. 1.5 g q12h) or consider continuous infusion (e.g. 3 g q24h); monitor trough concentrations to target concentrations of 15–25 mg/L
Teicoplanin	6 mg/kg q12h for 3 doses (LD) and 6 mg/kg q24h (MD)	6 mg/kg q12h for 3 doses	3–6 mg/kg q12h; monitor trough concentrations to target concentrations >15 mg/L
Other highly protein-bound drugs			
Daptomycin	4–6 mg/kg q24h		

LD = loading dose; **MD** = maintenance dose; **q*x*h** = every *x* hours.

Practical Tip: Hypoalbuminaemia (Alb < 25 g/l) is only likely to influence antibiotic PK when the agent is highly protein bound (>90%), and predominantly renally eliminated [69]. Examples include flucloxacillin, ertapenem, ceftriaxone and teicoplanin

THỪA CÂN Ở BỆNH NHÂN NẶNG VÀ CHẾ ĐỘ LIỀU KHÁNG SINH

Ảnh hưởng của thừa cân đến Dược động học kháng sinh



Al-Dorzi HM et al. Curr. Opin. Infect. Dis. 2014; 27: 165-173

THỪA CÂN Ở BỆNH NHÂN NẶNG VÀ CHẾ ĐỘ LIỀU KHÁNG SINH

	Hydrophilic antibiotics	Lipophilic antibiotics
Pharmacokinetics	▪ Generally have low volume of distribution. ▪ Are primarily cleared in kidneys. ▪ Have lower intracellular and tissue penetration.	▪ Generally have high volume of distribution. ▪ Are primarily cleared in the liver. ▪ Have higher intracellular and tissue penetration.
Changes in obesity	▪ Obesity has little effect of the antibiotic volume of distribution. ▪ Renal clearance is generally increased in obesity unless renal impairment is present.	▪ Obesity increases the antibiotic volume of distribution. ▪ Obesity have variable effects on hepatic clearance.
Dosing in obesity	Ideal or adjusted body weight is generally used for dosing[a].	Total body weight is generally recommended for dosing[a].

Weight descriptor formulae

$BMI = \text{weight in kg}/(\text{height in m})^2$

IBW for men = 50 kg + 2.3 kg for each inch above 60 inches of height

IBW for women = 45.5 kg + 2.3 kg for each inch above 60 inches of height

$ABW = IBW + [(C) \times (TBW - IBW)]$

C = correction factor, for hydrophilic drugs (0.37–0.58), average 0.4

Estimated LBW (Kg) for men $= (9270 \times TBW)/(6680 + 216 \times BMI)$

Estimated LBW (Kg) for women $= (9270 \times TBW)/(8780 + 244 \times BMI)$

uinolones
des
line

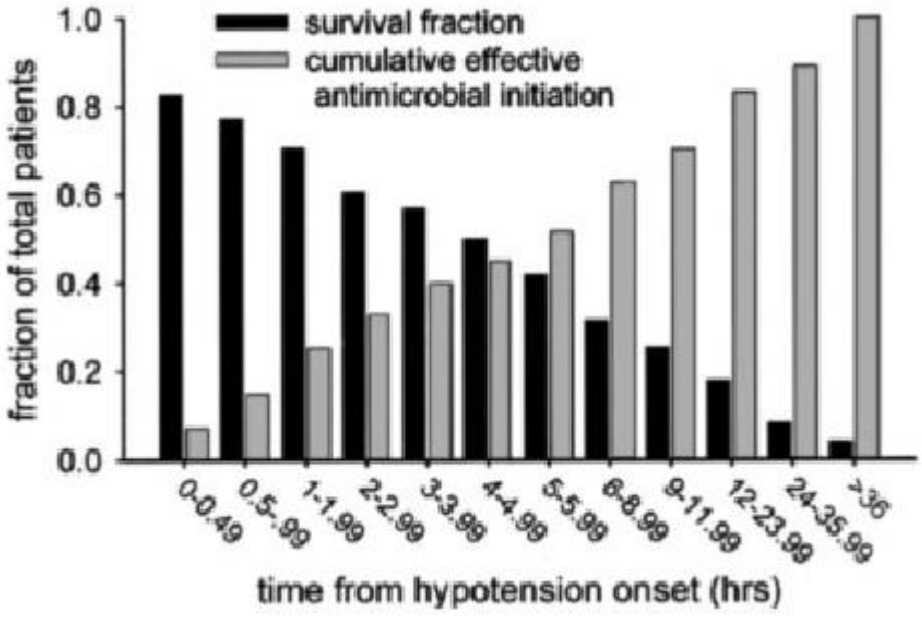
Al-Dorzi HM et al. Curr. Opin. Infect. Dis. 2014; 27: 165-173

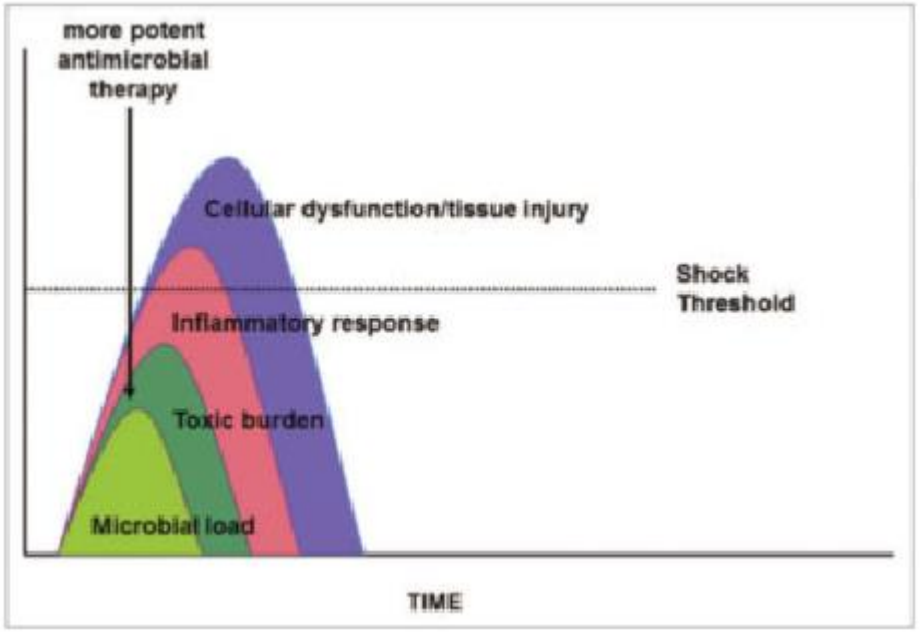
THỪA CÂN Ở BỆNH NHÂN NẶNG VÀ CHẾ ĐỘ LIỀU KHÁNG SINH

Antimicrobial class	Dosing recommendations in obese patients with pneumonia
Penicillins	Higher doses of piperacillin and tazobactam and longer infusion time of up to 4 h.
Cephalosporins	The upper limit of normal doses is recommended.
Carbapenems	The upper limit of normal doses with extended infusions over approximately 3–4 h is recommended.
Fluoroquinolones	Dose adjustment is probably not warranted for levofloxacin and moxifloxacin. Doses of up to 800 mg every 12 h of ciprofloxacin should be considered in morbidly obese patients.
Macrolides	Standard doses are recommended. Whether higher doses and longer durations should be used remains uncertain.
Aminoglycosides	The loading dose should be based on adjusted or lean body weight with subsequent dose and interval based on kidney function and drug level.
Vancomycin	The loading dose is 25–30 mg/kg of total body weight in seriously ill patients. Maintenance dose is 15–20 mg/kg of total body weight every 8–12 h, not to exceed 2 g per dose for patients with normal kidney function. Serum trough concentration should be measured prior to the fourth or fifth dose. Target trough concentrations of 15–20 μg/ml are recommended. Doses >1.5 g should be infused over ≥1.5 h.
Linezolid	Standard linezolid dosing with consideration of continuous infusion is recommended.
Colistin	Dosing colistin using ideal body weight is recommended. Loading doses are suggested.
Voriconazole	Dosing based on adjusted or ideal body weight is recommended.
Oseltamivir	Early standard oseltamivir dosing is recommended with dose increase to 150 mg every 12 h in severe disease and normal kidney function.

Al-Dorzi HM et al. Curr. Opin. Infect. Dis. 2014; 27: 165-173

Điều trị nhiễm trùng do VK Gram âm đa kháng: Tránh thiếu liều đầu kháng sinh





Tương tự nguyên tắc điều trị sepsis, thời gian là vàng với một phác đồ kháng sinh phù hợp (bao gồm cả chế độ liều phù hợp)

Vasquez-Grande G and Kumar A. Sem. Respr. Crit Care Med 2015; 36: 154-166

KHÔNG ĐẠT NỒNG ĐỘ KHÁNG SINH BETA-LACTAM SAU LIỀU ĐẦU TIÊN: LỢI ÍCH CỦA LIỀU NẠP

	meropenem (n = 16)	ceftazidime (n = 18)	cefepime (n = 19)	piperacillin-tazobactam (n = 27)
T > 4 × MIC (%)	57 (25-100)	45 (8-100)	34 (10-100)	33 (0-100)
Adequate PK, n (%)	12 (75)	5 (28)	3 (16)	12 (44)
CrCl <50 mL/min (%)	5/6 (83)	3/9 (33)	2/12 (17)	10/14 (71)
CrCl >50 mL/min (%)	7/10 (70)	2/9 (22)	1/7 (14)	2/13 (15) *

Data are expressed as counts (percentage) or median (range).
CrCl, creatinine clearance; MIC, minimal inhibitory concentration; PK, pharmacokinetic.
* $P = 0.03$ (vs. CrCl < 50 mL/min).

Tỷ lệ bệnh nhân không đạt nồng độ beta-lactam sau khi dùng liều đầu kháng sinh (2 g ceftazidim/cefepim, 4,5 g piperacillin/tazobactam, 1 g meropenem) ở bệnh nhân sepsis nặng và sốc sepsis (nghiên cứu trên 80 BN ICU tại 4 bệnh viện Bỉ)

Taccone FS et al. Crit. Care 2010; 14: R126

TĂNG THỂ TÍCH PHÂN BỐ Ở BỆNH NHÂN NẶNG: VAI TRÒ CỦA LIỀU NẠP

Practical Tip: Clinicians should consider use of higher initial doses of aminoglycosides [94], beta-lactams [99], glycopeptides [84], tigecycline [90] and colistin [100] in septic, critically ill patients. Subsequent dosing can then be modified on the basis of drug eliminating organ function.

Practical Tip: Continuous infusions should be commenced post loading dose at a point no further than halfway through the usual dosing interval. For convenience, we recommend starting the infusion at the conclusion of administration of the loading dose.

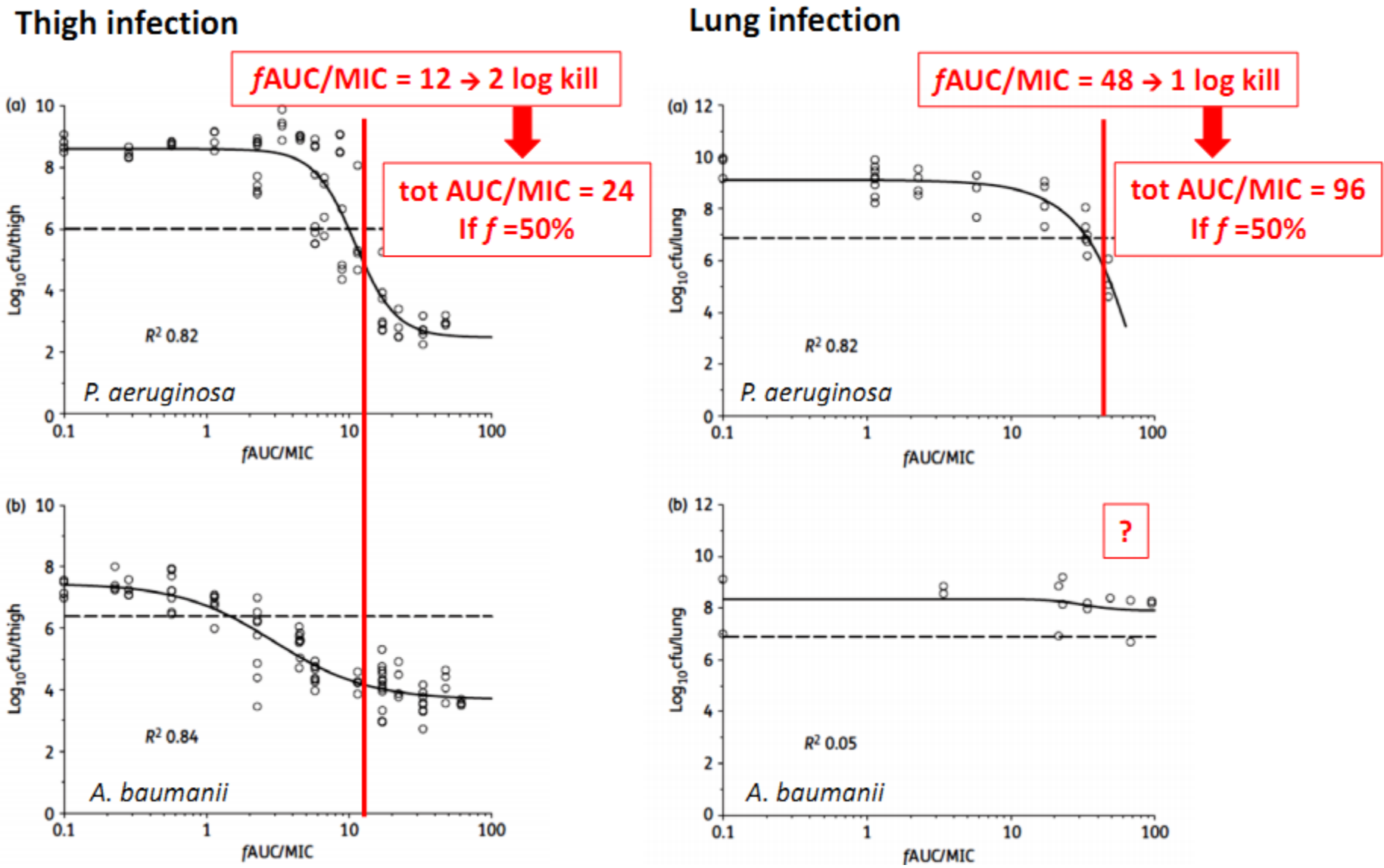
Udy AA et al. Intens. Care Med. 2013; 39: 2070-2082

VAI TRÒ CỦA LIỀU NẠP

Class of antibiotic	Initial empirical dose ('normal' renal function)
Aminoglycosides	Gentamicin 7 mg/kg ABW 24 hourly [4]
	Amikacin 30 mg/kg ABW 24 hourly [81]
	Dose adjusted by TDM [82]
Beta-lactams[a] [80]	Flucloxacillin 2 g 4 hourly
	Amoxycillin 2 g 4–6 hourly
	Ceftriaxone 1 g 12 hourly (2 g 12 hourly for CNS infection)
	Cefepime 2 g 8 hourly
	Ceftazidime 2 g 6–8 hourly
	Imipenem 0.5–1.0 g 6–8 hourly
	Piperacillin/tazobactam 4.5 g 4–6 hourly
	Ticarcillin/clavulanate 3.1 g 4–6 hourly
	Meropenem 1 g 6–8 hourly (2 g 6–8 hourly for CNS infection [83])
	Ertapenem 1 g 12 hourly
Glycopeptides	Vancomycin 35 mg/kg TBW loading dose followed by 30 mg/kg/day continuous infusion [84]
	Dose adjusted by TDM
	Teicoplanin 12 mg/kg 12 hourly × 3 doses, followed by 6–12 mg/kg 24 hourly [85]
	Dose adjusted by TDM
Fluoroquinolones	Ciprofloxacin 400 mg 8 hourly [86]
	Levofloxacin 750–1,000 mg 24 hourly [87]
	Moxifloxacin 400 mg 24 hourly [88]
Miscellaneous	Linezolid 600 mg 12 hourly [89]
	Daptomycin 8–12 mg/kg 24 hourly
	Lincosamides 600–900 mg 8 hourly
	Tigecycline 100 mg loading dose, followed by 50 mg 12 hourly (or 200 mg followed by 100 mg 12 hourly when borderline susceptibility is suspected) [90]
	Colistin—dosing according to Garonzik et al. [91]

Udy AA et al. Intens. Care Med. 2013; 39: 2070-2082

COLISTIN: DIỆT KHUẨN PHỤ THUỘC AUC/MIC



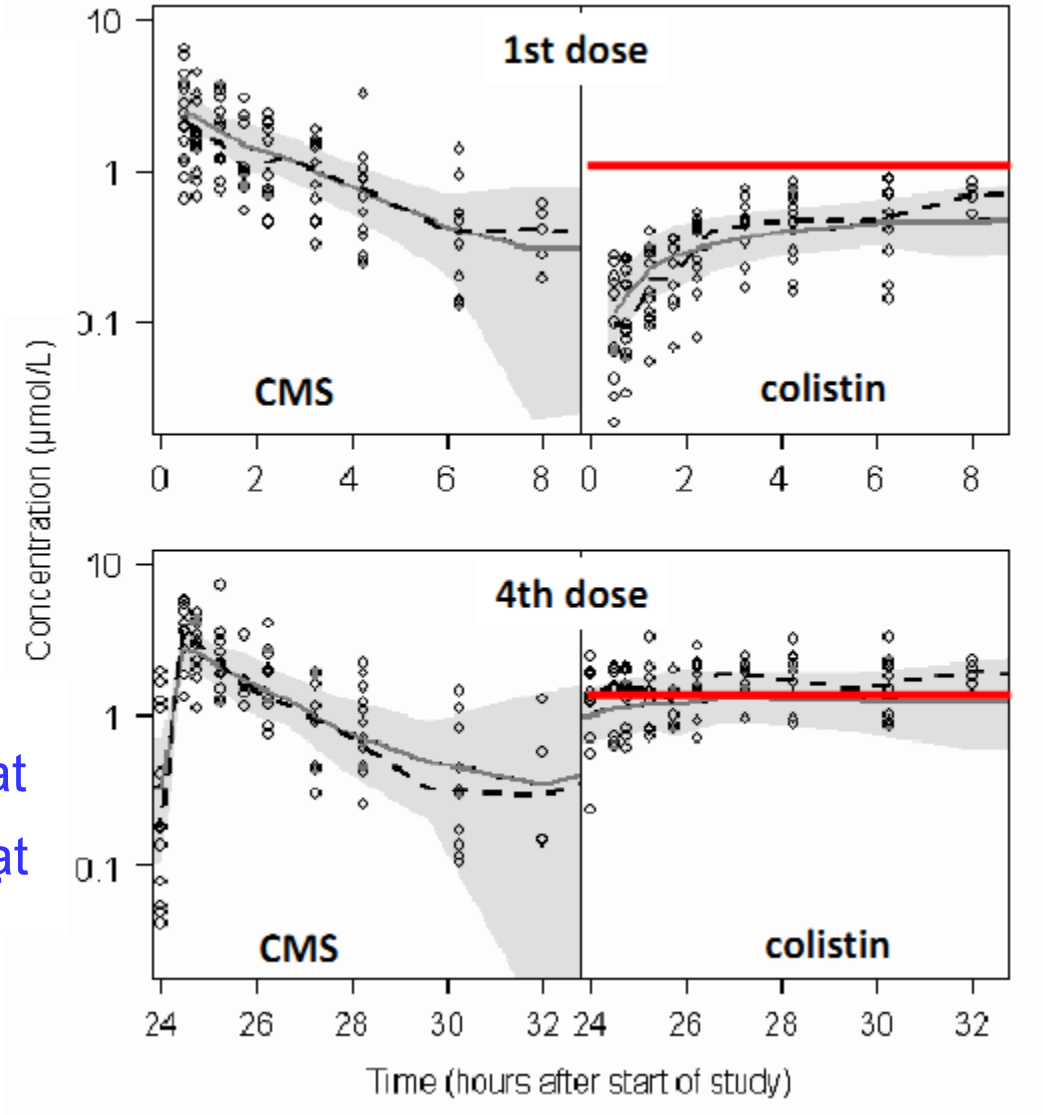
Cheah SE et al. J. Antimicrob. Chemother. 2015; 70: 3291-3297.

COLISTIN TRÊN BỆNH NHÂN NẶNG: LỢI ÍCH CỦA LIỀU NẠP

Dosage (colistin methane sulfonate [CMS]): 240 mg (3 x 10^6 U) every 8h

CMS
- $t_{1/2}$ ~ 2.3 h

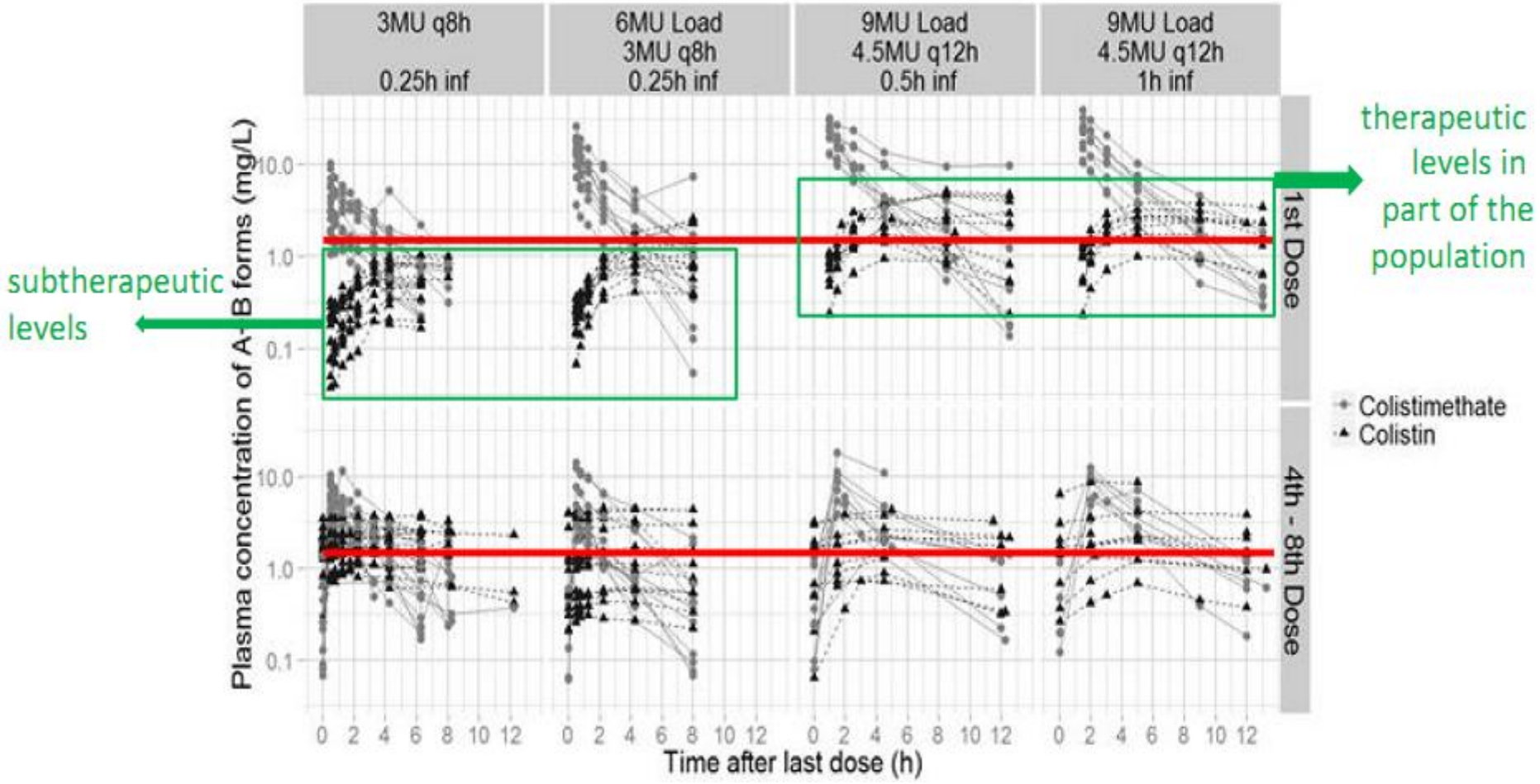
Colistin:
- $t_{1/2}$ ~ 14.4 h.
- Cmax
  - 1st dose: 0.60 mg/L
  - s.s.: 2.3 mg/L.



Colistin có t1/2 dài và không đạt đủ nồng độ điều trị trước khi đạt trạng thái ổn định ⇒ cần thiết phải dùng liều nạp

Plachouras et al. Antimicrob. Agents. Chemother. 2009; 53: 3430-3436.

COLISTIN TRÊN BỆNH NHÂN NẶNG: LỢI ÍCH CỦA LIỀU NẠP



Karaiskos I et al. Antimicrob. Agents. Chemother. 2015; 59: 7240-7248.

Cân nhắc sử dụng chế độ liều cao để cải thiện đáp ứng lâm sàng: colistin

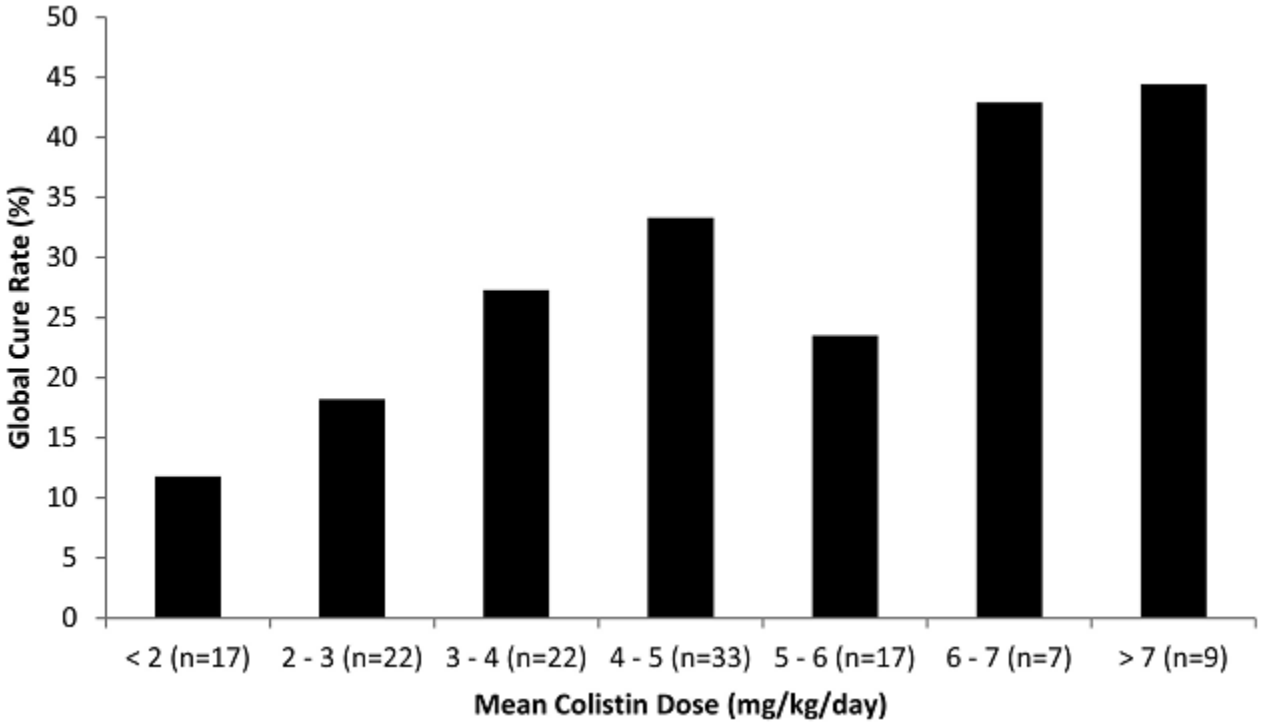


TABLE 3 Multivariate logistic regression analysis of day 7 global cure

Variable	Adjusted OR	95% CI	*P* value
High-dose colistin	3.40	1.37–8.45	0.008
Age (per year)	0.98	0.96–1.01	0.284
Gender (male)	1.32	0.57–3.1	0.516
Day 1 mechanical ventilation	1.28	0.48–3.4	0.625
Duration of colistin (per day)	0.99	0.93–1.05	0.747

Gibson GA et al. Antimicrob. Agents Chemother. 2016; 60: 431-436

Chế độ liều cao colistin: nghiên cứu lâm sàng

High-Dose, Extended-Interval Colistin Administration in Critically Ill Patients: Is This the Right Dosing Strategy? A Preliminary Study

Lidia Dalfino,[1] Filomena Puntillo,[1] Adriana Mosca,[2] Rosa Monno,[2] Maria Luigia Spada,[1] Sara Coppolecchia,[1] Giuseppe Miragliotta,[2] Francesco Bruno,[1] and Nicola Brienza[1]

[1]Anesthesia and Intensive Care Unit, Department of Emergeny and Organ Transplantion; and [2]Microbiology Section, Department of Interdisciplinary Medicine, University of Bari, Italy

(See the Editorial Commentary by Roberts and Lipman, on pages 1727–9.)

Background. Gram-negative bacteria susceptible only to colistin (COS) are emerging causes of severe nosocomial infections, reviving interest in the use of colistin. However, consensus on the most effective way to administer colistin has not yet been reached.

Methods. All patients who had sepsis due to COS gram-negative bacteria or minimally susceptible gram-negative bacteria and received intravenous colistimethate sodium (CMS) were prospectively enrolled. The CMS dosing schedule was based on a loading dose of 9 MU and a 9-MU twice-daily fractioned maintenance dose, titrated on renal function. For each CMS course, clinical cure, bacteriological clearance, daily serum creatinine clearance, and estimated creatinine clearance were recorded.

Results. Twenty-eight infectious episodes due to *Acinetobacter baumannii* (46.4%), *Klebsiella pneumoniae* (46.4%), and *Pseudomonas aeruginosa* (7.2%) were analyzed. The main types of infection were bloodstream infection (64.3%) and ventilator-associated pneumonia (35.7%). Clinical cure was observed in 23 cases (82.1%). Acute kidney injury developed during 5 treatment courses (17.8%), did not require renal replacement therapy, and subsided within 10 days from CMS discontinuation. No correlation was found between variation in serum creatinine level (from baseline to peak) and daily and cumulative doses of CMS, and between variation in serum creatinine level (from baseline to peak) and duration of CMS treatment.

Conclusions. Our study shows that in severe infections due to COS gram-negative bacteria, the high-dose, extended-interval CMS regimen has a high efficacy, without significant renal toxicity.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 October 2014
EMA/643444/2014

European Medicines Agency completes review of polymyxin-based medicines

Recommendations issued for safe use in patients with serious infections resistant to standard antibiotics

- injection or infusion (drip) of colistimethate sodium should be reserved for the treatment of serious infections due to susceptible bacteria, in patients whose other treatment options are limited.
- colistin should be given with another suitable antibiotic where possible.
- Critically ill patients should be given a higher starting dose (loading dose) to provide an effective level of the antibiotic in the body more quickly.
  - recommended dose in adults is **9 million IU daily in 2 or 3 divided doses** as a slow intravenous infusion; in critically ill patients a **loading dose of 9 million IU** should be given.
  - In children, the suggested dose is **75,000 to 150,000 IU/kg daily, in 3 divided doses.**

PHÂN TÍCH HIỆU QUẢ VÀ ĐỘC TÍNH TRÊN THẬN CỦA CHẾ ĐỘ LIỀU CAO COLISTIN TRÊN BỆNH NHÂN NHIỄM TRÙNG BỆNH VIỆN TẠI KHOA HỒI SỨC TÍCH CỰC, BỆNH VIỆN BẠCH MAI

Đào Xuân Cơ*, Nguyễn Đăng Tuân*
Phạm Hồng Nhung*, Đỗ Thị Hồng Gấm*, Dương Thanh Hải*
Nguyễn Gia Bình*, Nguyễn Hoàng Anh,**
Vũ Đình Hòa, Bùi Thị Hảo****

Chỉ tiêu	Kết quả
Tỷ lệ đáp ứng lâm sàng, n (%)	31 (70.5)
Tỷ lệ đáp ứng vi sinh, n (%)	31 (70.5)
Tỷ lệ đáp ứng cả lâm sàng và vi sinh, n (%)	23 (52.3)
Tỷ lệ tử vong, n (%)	
Tỷ lệ tử vong ngày 14	0 (0.0)
Tỷ lệ tử vong ngày 28	4 (9.1)
Tỷ lệ tử vong tại HSTC	5 (11.4)
Tỷ lệ xuất hiện độc tính trên thận, n (%)	14 (31.8)

colistin. Tuổi cao, điểm SOFA và APACHE II cao, nhiễm khuẩn nặng và có suy thận trước khi dùng thuốc là các yếu tố làm giảm hiệu quả điều trị của phác đồ này.

NGHIÊN CỨU ĐỘC TÍNH THẬN TRÊN BỆNH NHÂN SỬ DỤNG COLISTIN TẠI KHOA HỒI SỨC TÍCH CỰC BỆNH VIỆN BẠCH MAI

Đào Xuân Cơ[1], Dương Thanh Hải[1], Trần Nhân Thắng[1],
Đỗ Thị Hồng Gấm[1], Vũ Đình Hòa[2], Nguyễn Hoàng Anh[2].

Bảng 3.5. Kết quả phân tích các yếu tố nguy cơ theo phương pháp hồi quy Cox đa biến

YTNC nghiên cứu	Theo thời gian dùng thuốc		Theo liều colistin tích lũy	
	HR hiệu chỉnh CI 95%	p	HR hiệu chỉnh CI 95%	p
Tuổi	-		1,03 (1,01 – 1,05)	**0,020**
Cân nặng (kg)	1,05 (1,01 – 1,09)	**0,009**	1,05 (1,02 – 1,09)	**0,003**
Sốc nhiễm khuẩn	-		-	
Điểm Charlson	-		-	
Tăng bilirubin	4,14 (0,90 – 19,06)	0,068	7,90 (1,63 – 38,22)	**0,010**
Liều colistin ≥ 4mg/kg/ngày	3,10 (1,41 – 6,81)	**0,005**	-	-
Dùng kèm thuốc lợi tiểu	2, 54 (0,92 – 7,00)	0,072	3,03 (1,08 – 8,50)	**0,035**
Dùng kèm thuốc vận mạch	2,65 (1,21 - 5,80)	**0,015**	2,79 (1,27 -6, 14)	**0,011**

Xây dựng chế độ liều mới cho colistin cân bằng hiệu quả/độc tính thận

Vancomycin

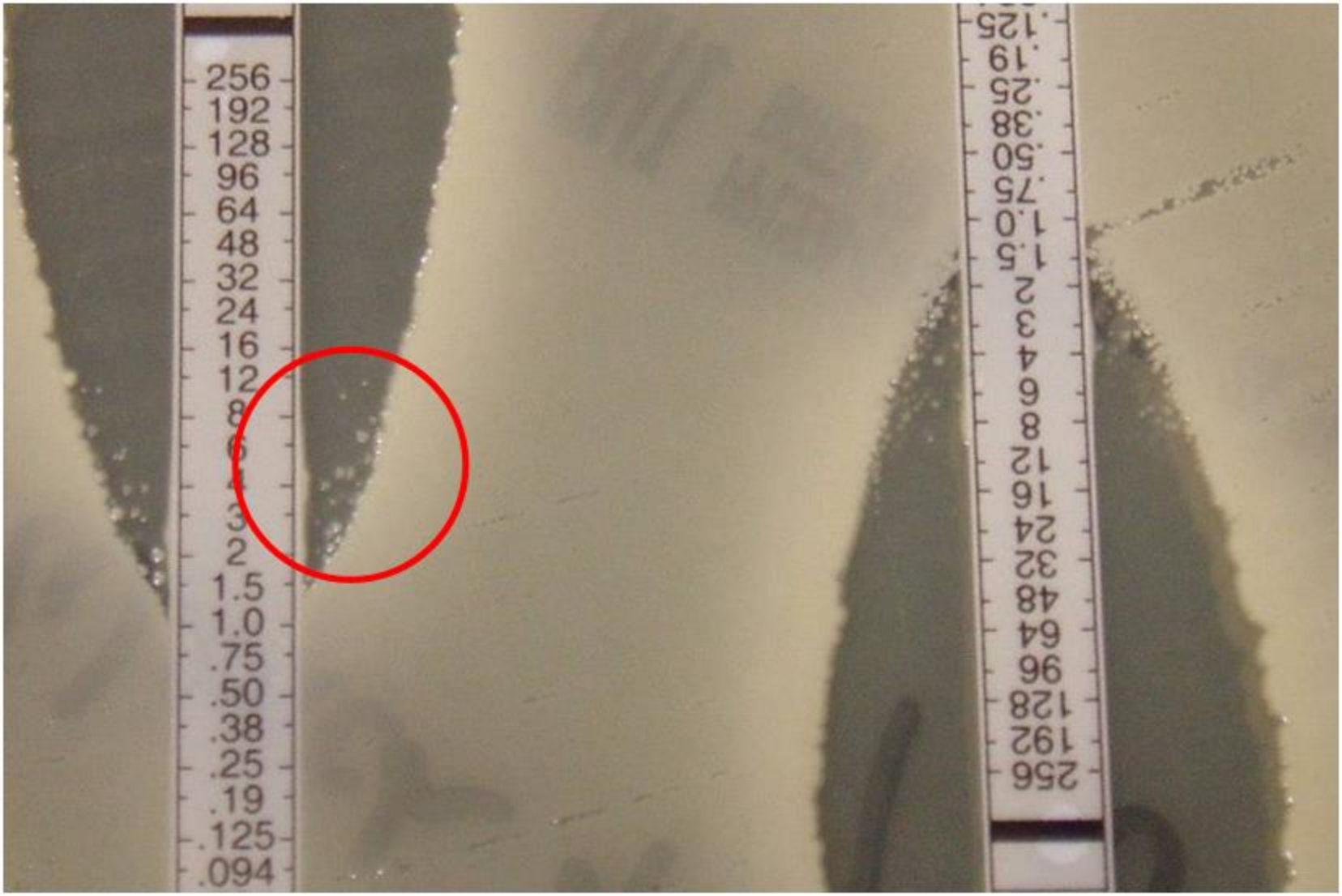
- Phát hiện năm 1953
- Được sử dụng trở lại từ những năm 1980 để điều trị nhiễm trùng do MRSA
- Thay đổi độ nhạy cảm theo thời gian

Susceptible	Intermediate	Resistant
≤4 µg/mL	8 – 16 µg/mL	≥ 32 µg/mL
↓	↓	↓
≤2 µg/mL	4 – 8 µg/mL	≥ 16 µg/mL

MIC

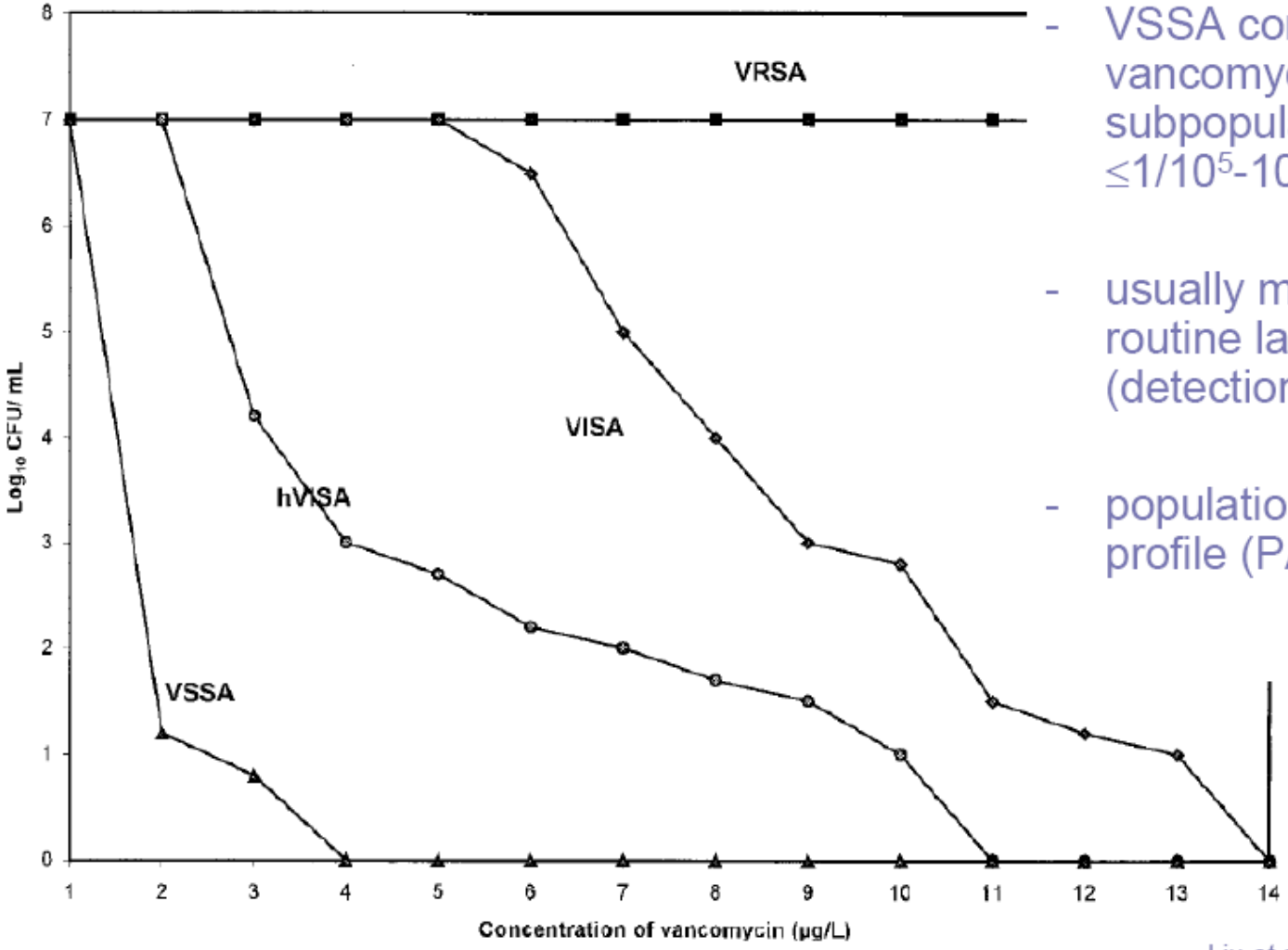
EUCAST breakpoint

Giảm nhạy cảm và đề kháng VAN trên lâm sàng (VISA): phát hiện thông qua E-test



Giảm nhạy cảm và đề kháng VAN trên lâm sàng

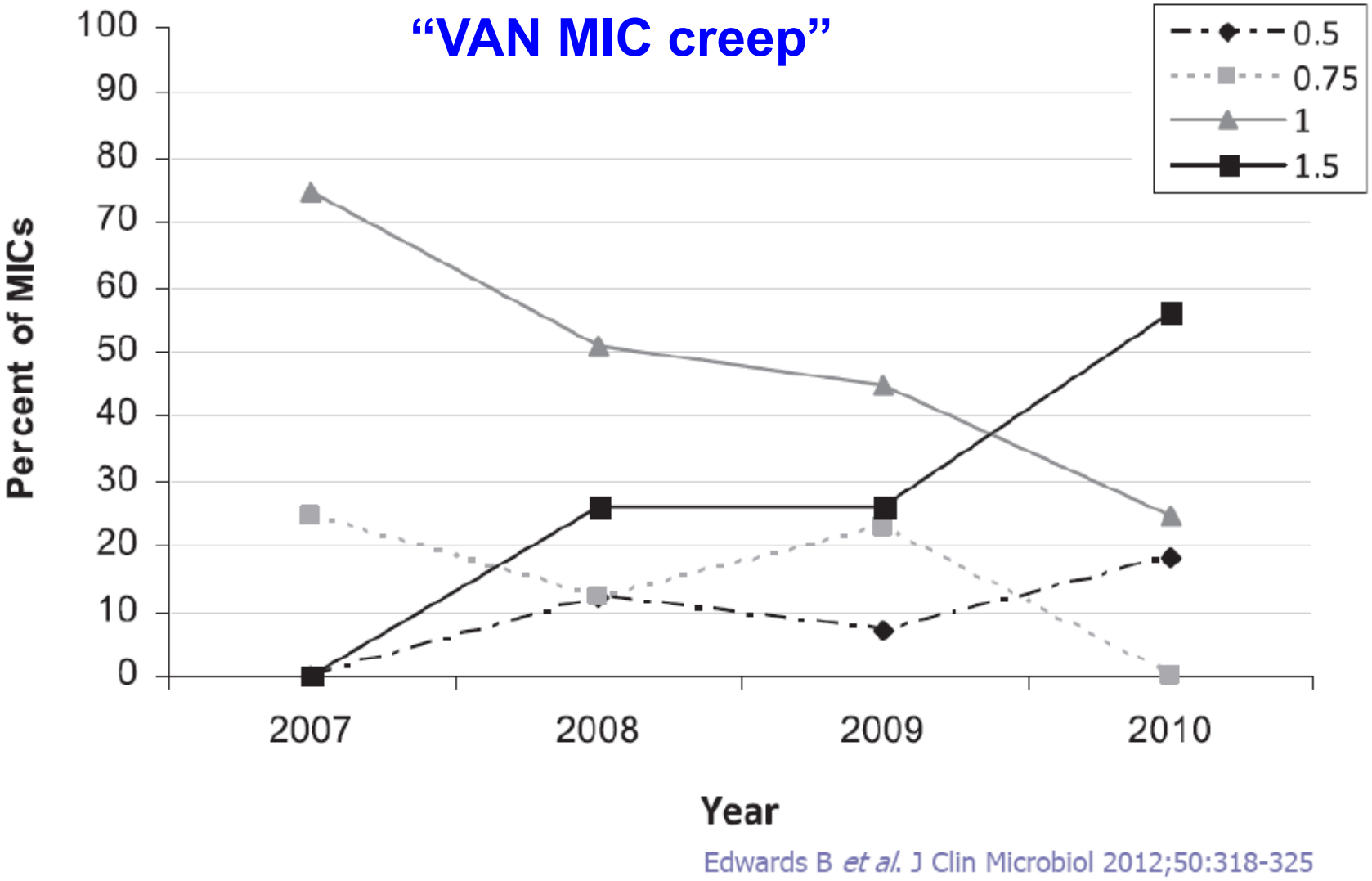
hVISA =heterogenous vancomycin intermediary susceptible *S. aureus*



- VSSA containing vancomycin resistant subpopulations (usually $\leq 1/10^5$-10^6)
- usually missed by routine lab techniques (detection limit 10^4)
- population analysis profile (PAP)

Liu *et al, AAC*, 2003,47:3040-5.

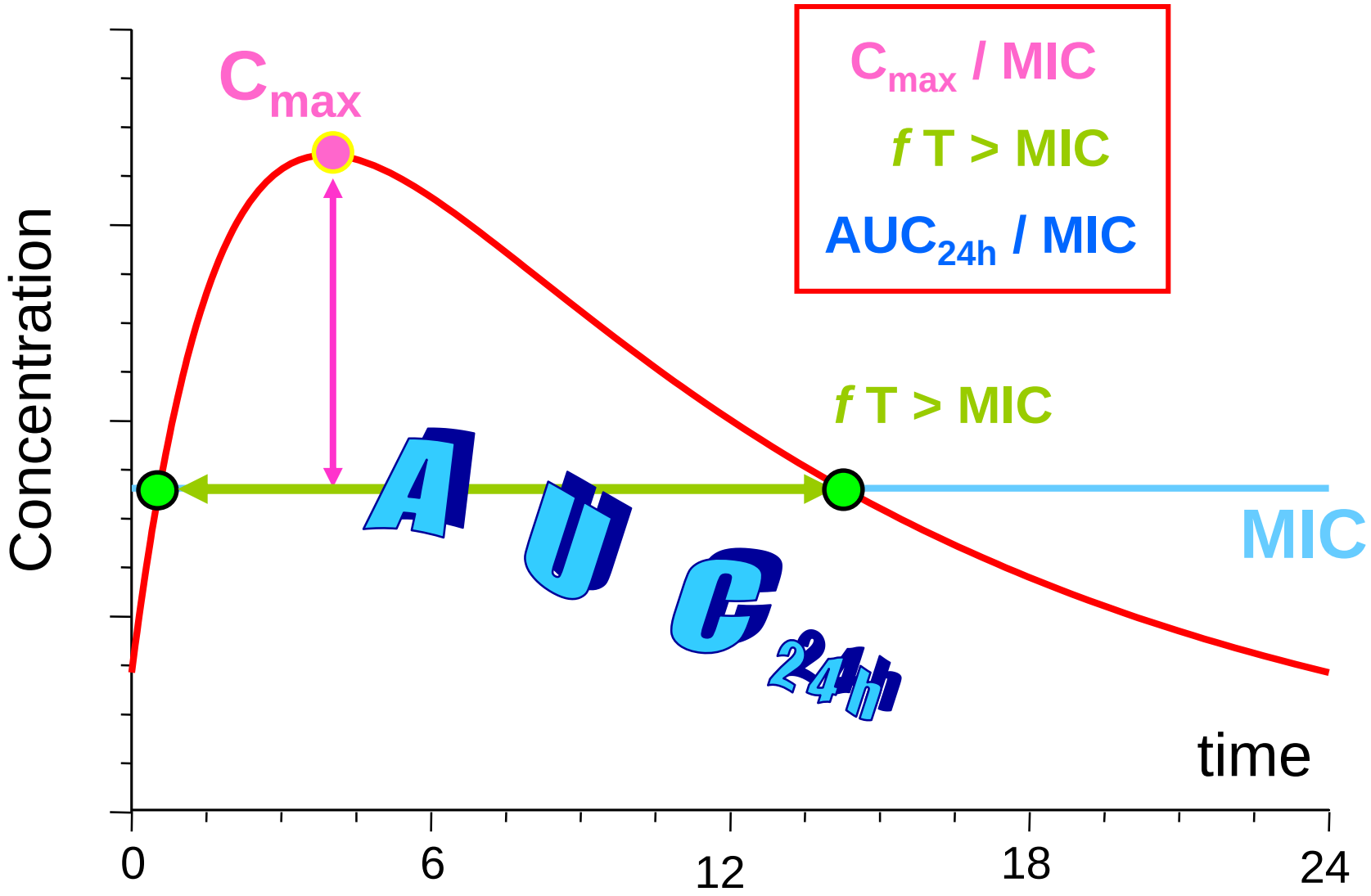
Giảm nhạy cảm và đề kháng VAN trên lâm sàng



Edwards B *et al.* J Clin Microbiol 2012;50:318-325

PK/PD ÁP DỤNG CHO VANCOMYCIN Ở BỆNH NHÂN NẶNG

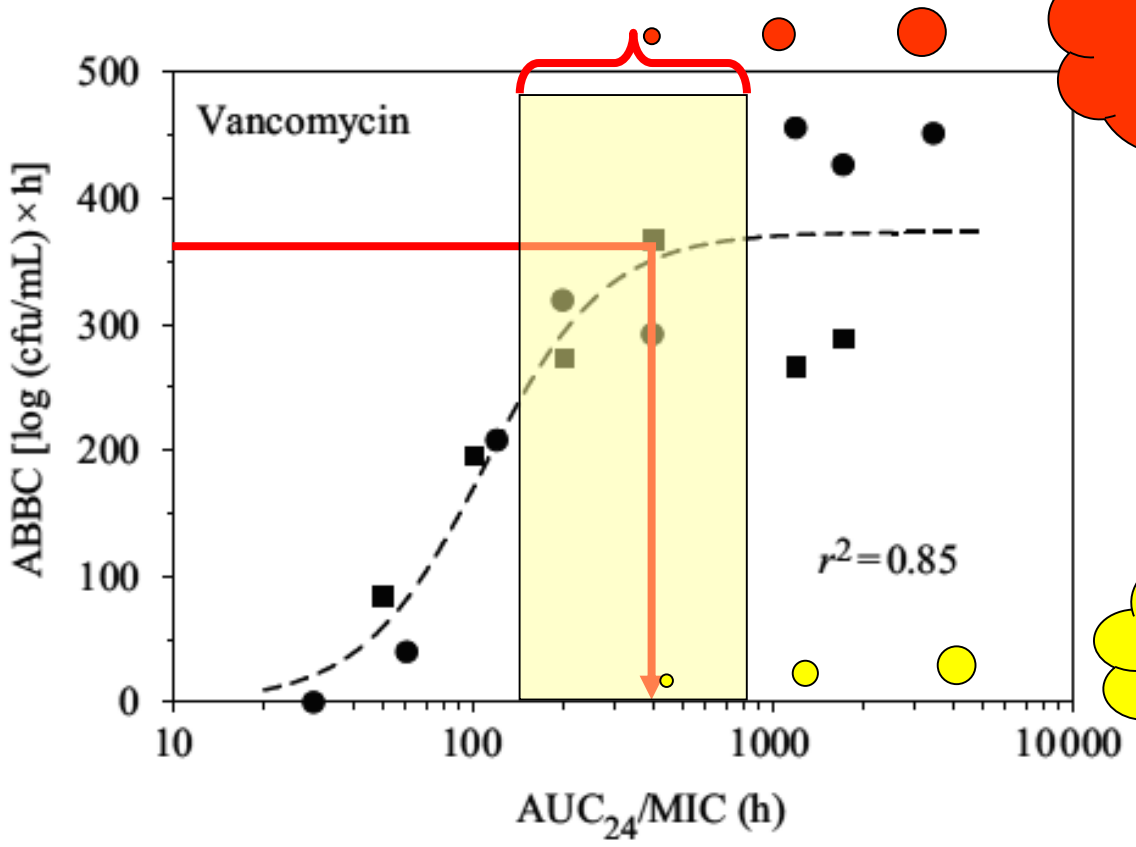
- **VAN là kháng sinh phụ thuộc AUC_{24h}/MIC**



Vancomycin AUC24h *in vitro*

Mô hình *in vitro* mô phỏng PK trên bệnh nhân

Hiệu quả



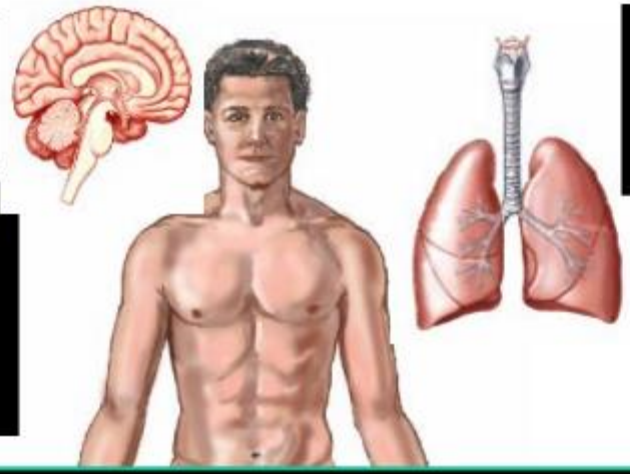
Dao động trên BN (160-783)

Cần ít nhất 400 !

Phơi nhiễm thuốc

Lubenko et al. J Antimicrob Chemother. 2008; 62:1065-9.

Tại sao cần AUC/MIC lớn như vậy?



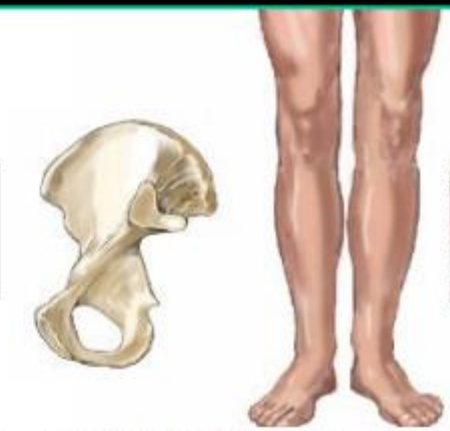
CNS: <10%

Sternal bone[1]: 57%
Heart valve[4]: 12%

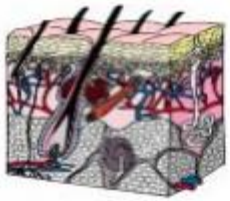
Epithelial lining fluid[3]: 18%

Lung tissue[2]: 17%–24%

Vancomycin Tissular Penetration is poor



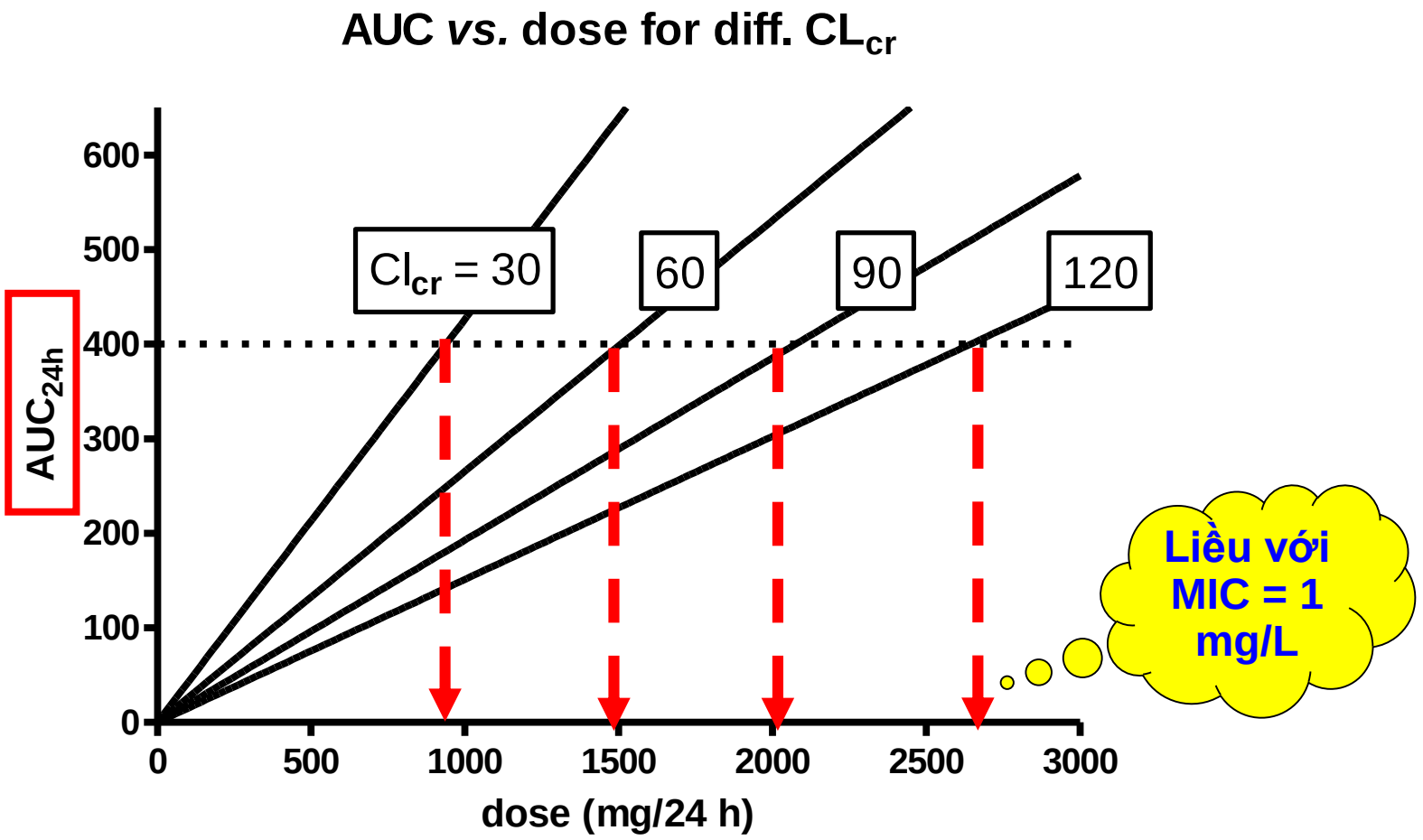
Bone[5]: 7%–13%



Fat[4]: 14%
Muscle[4]: 9%

1. Massias L et al. *Antimicrob Agents Chemother*. 1992;36:2539-2541. 2. Cruciani M et al. *J Antimicrob Chemother*. 1996;38:865-869. 3. Lamer C et al. *Antimicrob Agents Chemother*. 1993;37:281-286. 4. Daschner FD et al. *J Antimicrob Chemother*. 1987;19:359-362. 5. Graziani AL et al. *Antimicrob Agents Chemother*. 1988;32:1320-1322.

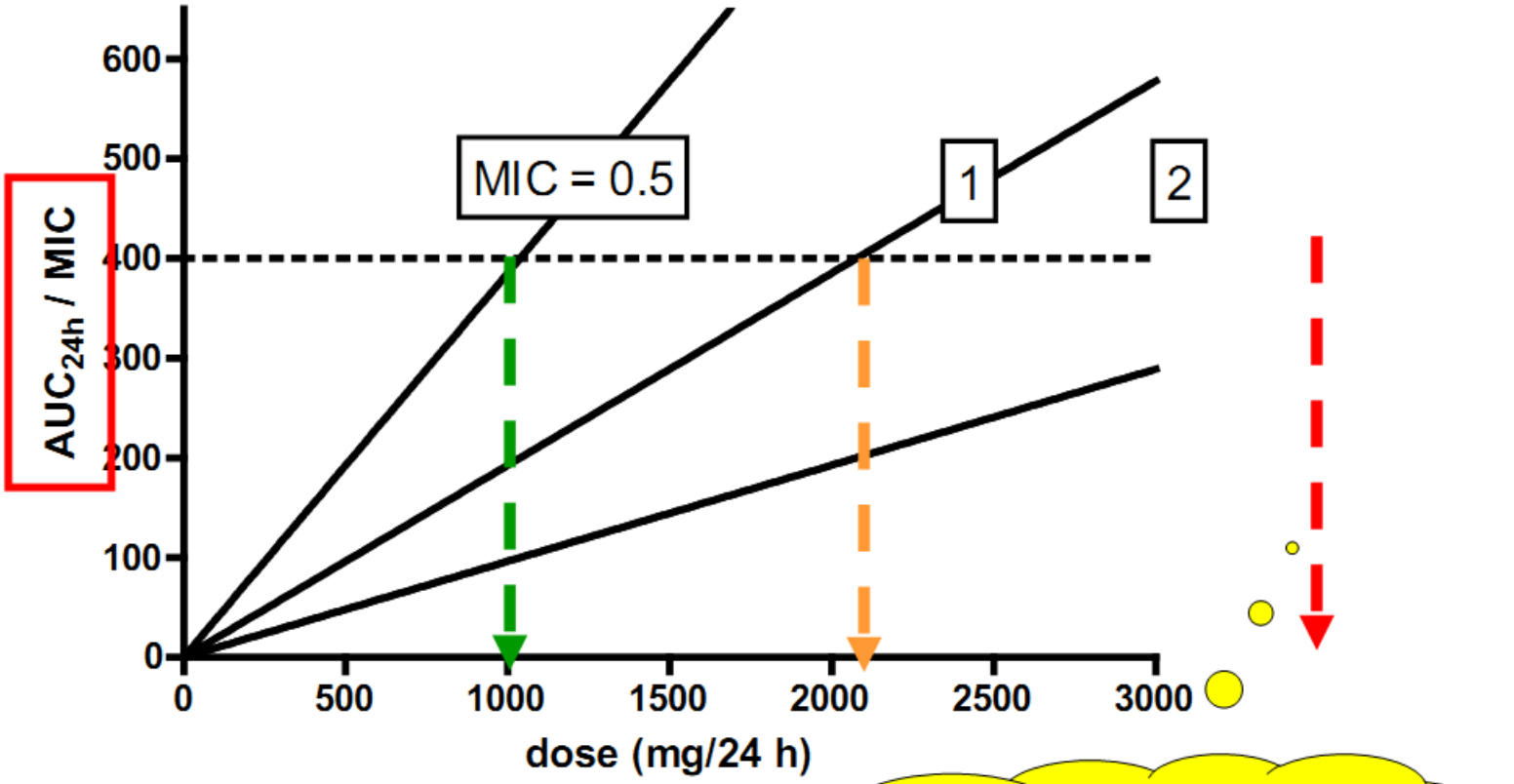
Tính AUC_{24h}?



$$AUC_{24} = \frac{D}{[(CL_{CR} \times 0.79) + 15.4] \times 0.06}$$

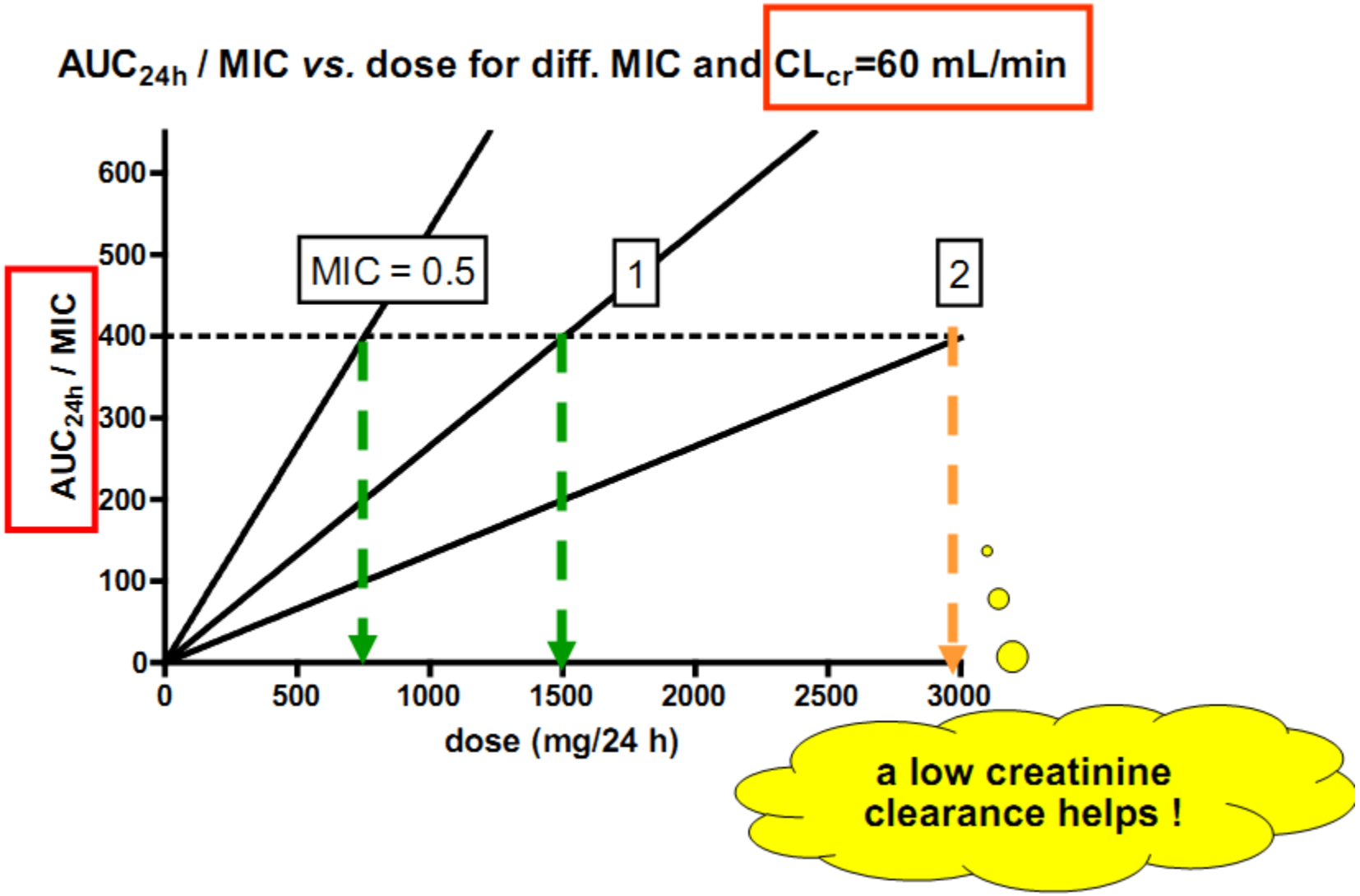
Moise-Broder *et al.* Clin. Pharmacokinet. 2004; 43:925-942

Chế độ liều 1 g q12 h chỉ phù hợp với MIC≤ 1



Moise-Broder *et al.* Clin. Pharmacokinet. 2004; 43:925-942

BN có thanh thải creatinin thấp dễ đạt AUC/MIC hơn với các chế độ liều hiện tại



PK/PD của VAN: mô phỏng Monte Carlo

Monte Carlo analysis on 37 patients
Probability of target achiement

CLCR	20	40	60	80	100	120 ml/min
500 mg IV every 12 h						
0.5 mg/L	94%	87%	75%	61%	49%	39%
1.0 mg/L	77%	49%	29%	17%	10%	6%
2.0 mg/L	29%	8%	2%	1%	0.3%	0.2%
1000 mg IV every 12 h						
0.5 mg/L	98%	97%	95%	92%	86%	80%
1.0 mg/L	94%	87%	75%	61%	49%	39%
2.0 mg/L	77%	49%	29%	17%	10%	6%
1500 mg IV every 12 h						
0.5 mg/L	99%	98%	98%	97%	96%	93%
1.0 mg/L	97%	95%	90%	82%	74%	66%
2.0 mg/L	89%	75%	57%	42%	30%	22%
2000 mg IV every 12 h						
0.5 mg/L	99%	99%	99%	99%	98%	97%
1.0 mg/L	98%	97%	95%	92%	87%	81%
2.0 mg/L	94%	87%	75%	61%	49%	39%

MIC

Patel *et al.* Clin Infect Dis 2011;52:969–974

Nồng độ đích cần đạt của VAN (2011)

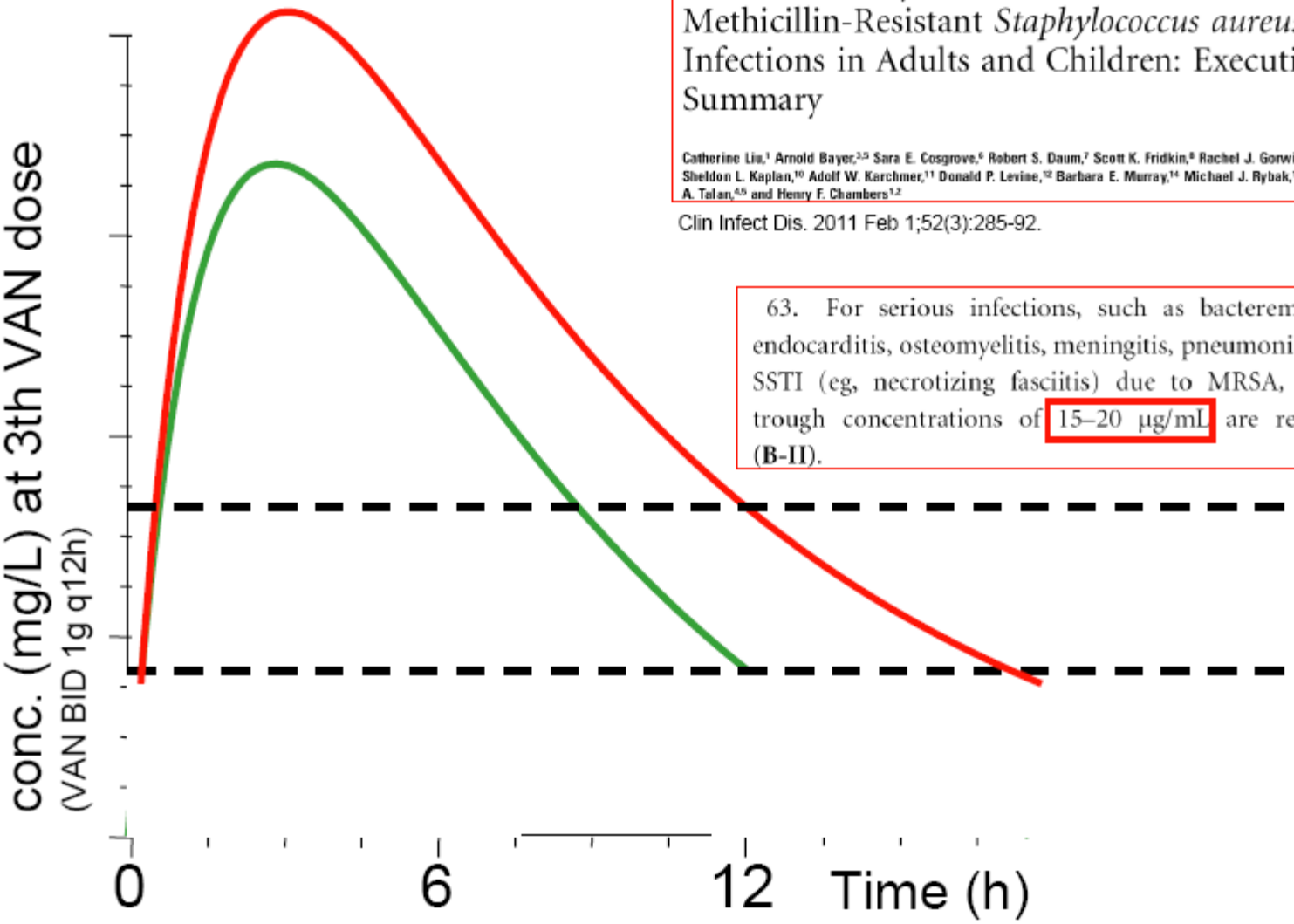
IDSA GUIDELINES

Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections in Adults and Children: Executive Summary

Catherine Liu,[1] Arnold Bayer,[2,3] Sara E. Cosgrove,[4] Robert S. Daum,[7] Scott K. Fridkin,[8] Rachel J. Gorwitz,[9] Sheldon L. Kaplan,[10] Adolf W. Karchmer,[11] Donald P. Levine,[12] Barbara E. Murray,[14] Michael J. Rybak,[12,13] David A. Talan,[5,6] and Henry F. Chambers[1,2]

Clin Infect Dis. 2011 Feb 1;52(3):285-92.

63. For serious infections, such as bacteremia, infective endocarditis, osteomyelitis, meningitis, pneumonia, and severe SSTI (eg, necrotizing fasciitis) due to MRSA, vancomycin trough concentrations of 15–20 μg/mL are recommended (**B-II**).



Vai trò của việc đạt nồng độ đích mới trong thực hành

ORIGINAL ARTICLE INFECTIOUS DISEASES

Association of vancomycin serum concentrations with efficacy in patients with MRSA infections: a systematic review and meta-analysis

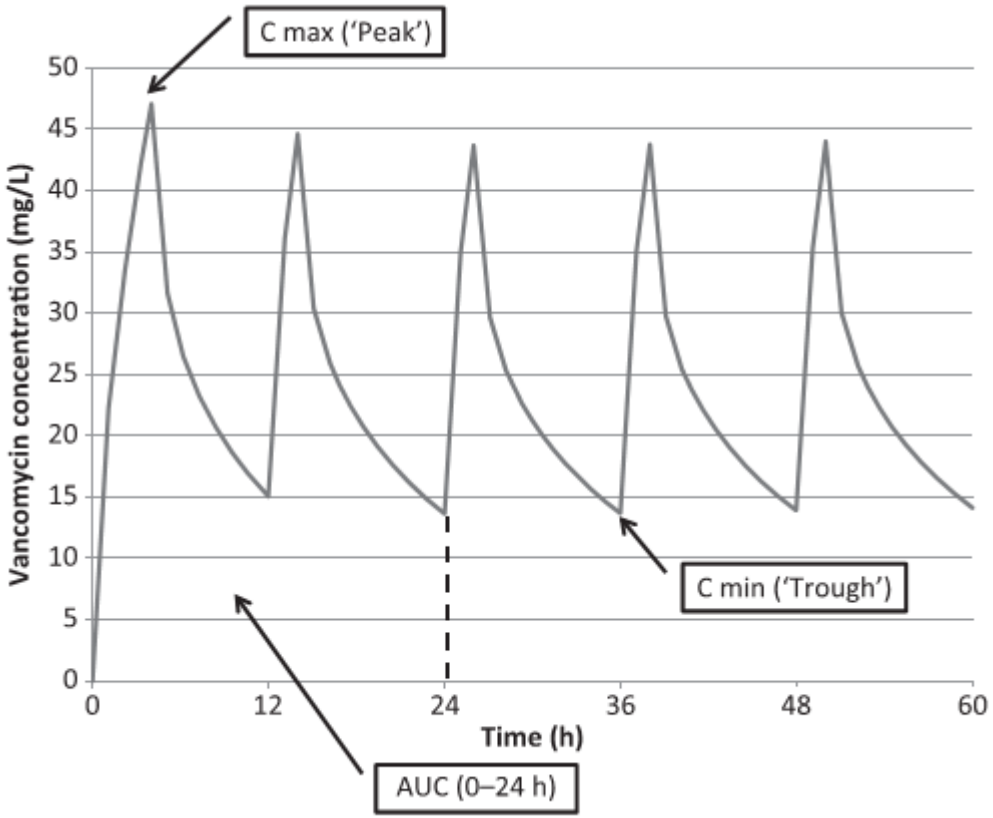
T. Steinmetz[1], N. Eliakim-Raz[2,3], E. Goldberg[2,3], L. Leibovici[1,3] and D. Yahav[2,3]

1) Department of Medicine E, 2) Infectious Diseases Unit, Rabin Medical Center, Beilinson Hospital, Petah-Tiqva and 3) Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

infections treatment. Four prospective and 12 retrospective studies were included (2003 participants). No significant difference was demonstrated between low and high vancomycin trough level for the outcome of all-cause mortality (odds ratio (OR) 1.07, 95% confidence interval (CI) 0.78–1.46, I^2 = 28%). In studies evaluating mainly MRSA pneumonia, there was significantly higher mortality with low vancomycin level (OR 1.78, 95% CI 1.11–2.84). No significant difference was demonstrated in treatment failure rates (OR 1.25, 95% CI 0.88–1.78, I^2 = 51%). However, excluding one outlier study from the analysis, treatment failure became significantly higher in patients with low vancomycin trough level (OR 1.46, 95% CI 1.12–1.91, I^2 = 16%). Microbiologic failure rates were significantly higher in patients with low vancomycin levels (OR 1.56, 95% CI 1.08–2.26, I^2 = 0%). Nephrotoxicity was significantly higher with vancomycin levels of ≥15 mg/L. However, no cases of irreversible renal damage were reported. Current data on the effectiveness of higher vancomycin trough levels in the treatment of MRSA infections are limited to few prospective and mainly retrospective studies. Our findings support the current recommendations for maintaining vancomycin trough levels of ≥15 mg/L in the treatment of severe MRSA infections, although no difference in all-cause mortality was observed.

Clin Microbiol Infect 2015; **21:** 665–673

Vai trò của liều nạp VAN



Thông số PK mô phỏng của VAN trên 1 bệnh nhân nam 60 tuổi, 70 kg, creatinin 80 µmol/L sau khi truyên liều nạp 2 g sau đó duy trì 1 g q12h

Vai trò của liều nạp VAN

Annals of Pharmacotherapy
2015, Vol. 49(5) 557–565

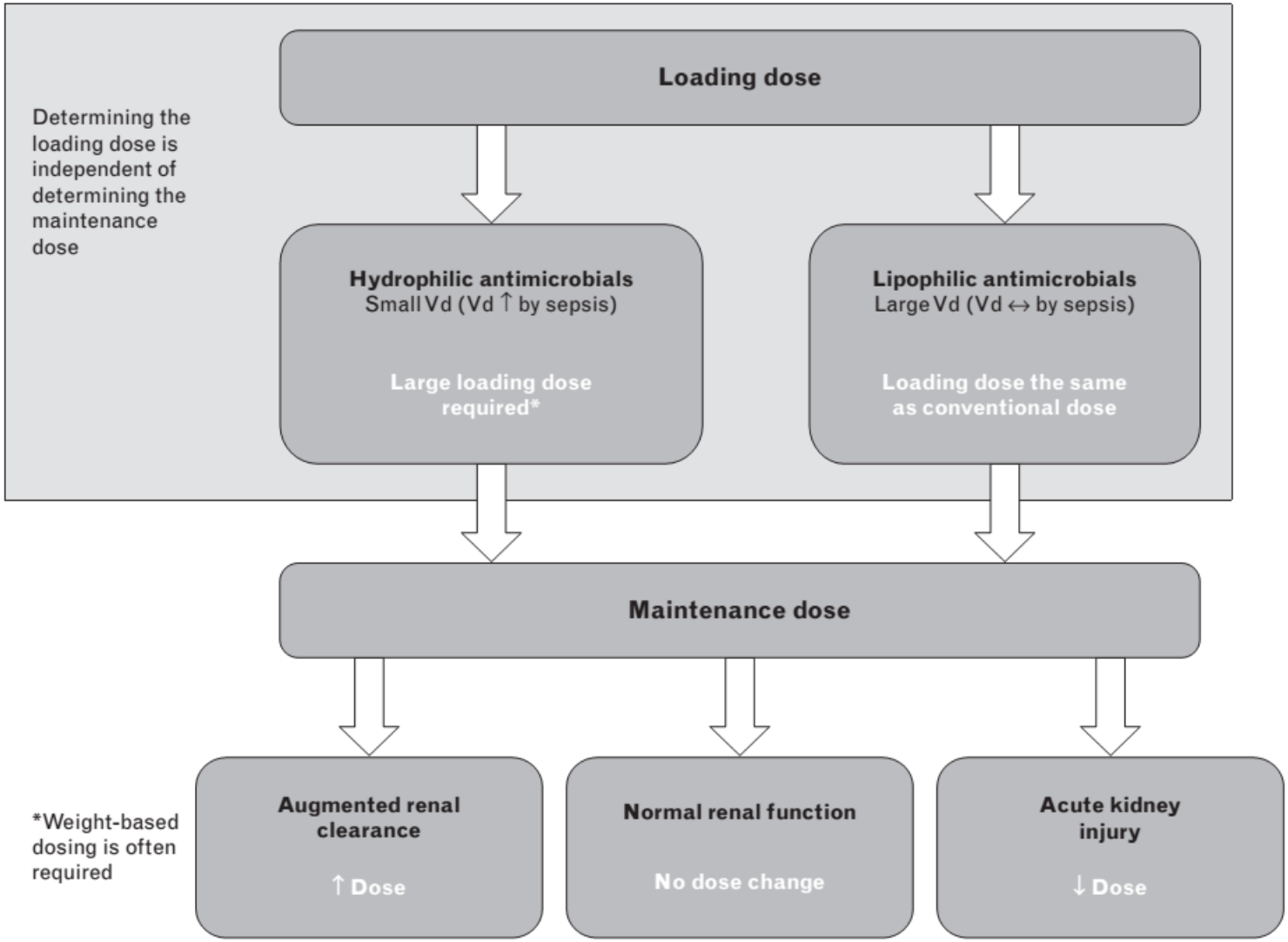
DOI: 10.1177/1060028015571163
aop.sagepub.com
SAGE

Vancomycin Loading Doses: A Systematic Review

Jillian Reardon[1], Tim T. Y. Lau, PharmD[1,2], and Mary H. H. Ensom, PharmD[1,3]

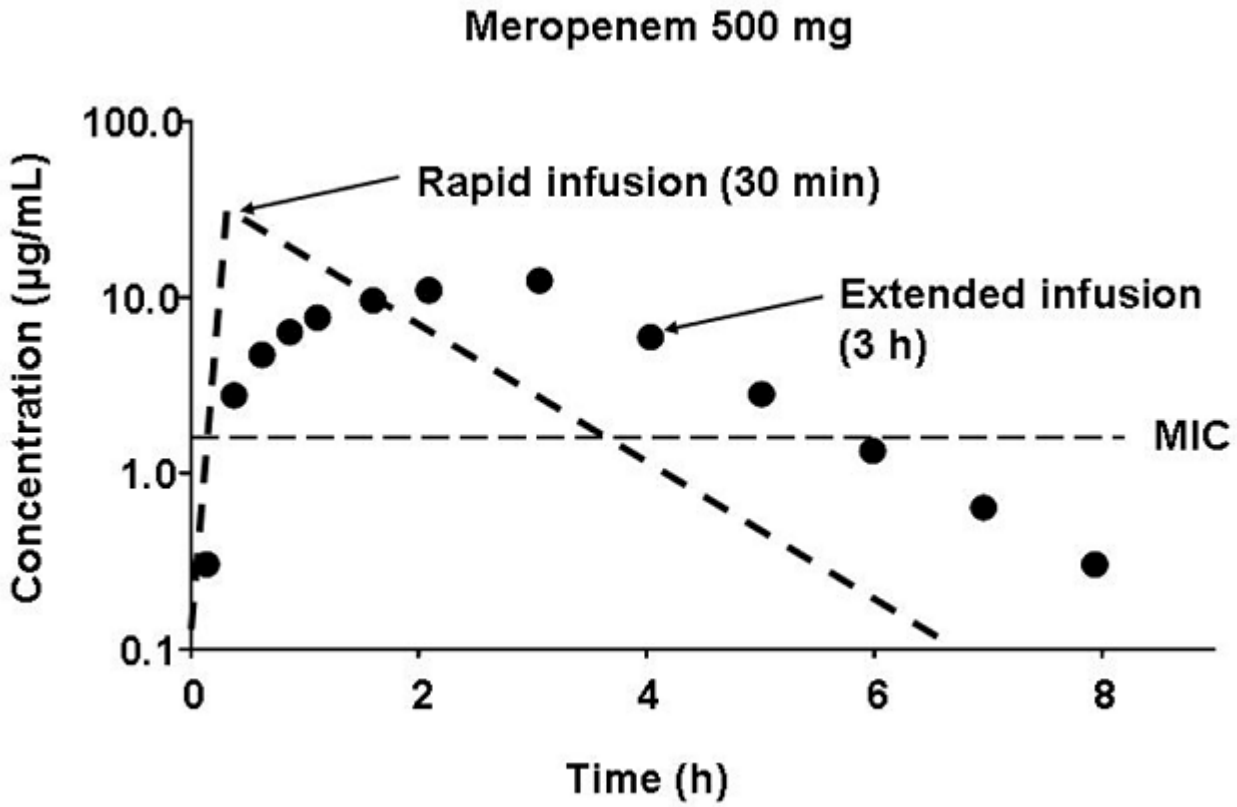
included heterogeneity and inconsistent timing of concentration measurements. **Conclusions:** High-quality data to guide the use of vancomycin LDs are lacking. LDs may more rapidly attain vancomycin troughs of 15 to 20 mg/L in adults, but information in pediatrics, obesity, and renal impairment is limited. Further studies are required to determine benefit of LDs on clinical and microbiological outcomes.

Thay đổi sinh lý bệnh liên quan đến PK của kháng sinh ở bệnh nhân nặng: liều nạp và liều duy trì



Tsai D et al. Curr. Opin. Crit. Care 2015; 21: 412-420

Truyền tĩnh mạch liên tục/kéo dài



Truyền tĩnh mạch kéo dài làm tăng T>MIC: kết quả với meropenem

Dandekar PK et al. Pharmacotherapy 2003; 23: 988_991

Intensive Care Med
DOI 10.1007/s00134-015-4188-0

ORIGINAL

Mohd H. Abdul-Aziz
Helmi Sulaiman
Mohd-Basri Mat-Nor
Vineya Rai
Kang K. Wong
Mohd S. Hasan
Azrin N. Abd Rahman
Janattul A. Jamal
Steven C. Wallis
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Christine E. Staatz
Jason A. Roberts

Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis

Primary endpoint	Intervention ($n = 70$)	Control ($n = 70$)	Absolute difference (95 % CI)	Significance (p value)[a,b]
Clinical cure for ITT population, n (%)	39 (56)	24 (34)	22 (−0.4 to −0.1)	**0.011**
Clinical cure by antibiotic, n (%)[c]				
Piperacillin/tazobactam	22 (58)	15 (32)	26 (−0.4 to −0.1)	**0.016**
Meropenem	14 (67)	8 (38)	29 (−0.5 to 0.1)	0.064
Cefepime	3 (27)	1 (50)	23 (−0.3 to 0.7)	1.000
Clinical cure by concomitant antibiotic treatment, n (%)[d]				
Yes	14 (42)	13 (39)	3 (−0.3 to 0.2)	0.802
No	25 (68)	11 (30)	38 (−0.6 to −0.2)	**0.001**
Clinical cure by site of infection, n (%)[e]				
Lung	27 (59)	12 (33)	25 (−0.4 to −0.1)	**0.022**
Clinical cure by *A. baumannii* or *P. aeruginosa* infection, n (%)[f]				
Yes	13 (52)	6 (25)	27 (−0.5 to 0.1)	0.052
No	10 (44)	12 (38)	6 (−0.3 to 0.2)	0.655

Secondary endpoints	Intervention ($n = 70$)	Control ($n = 70$)	Absolute difference (95 % CI)	Significance (p value)[a,b]
PK/PD target attainment, n (%)[g]				
50 % $fT_{>MIC}$ on day 1	56 (98)	49 (93)	5 (−0.2 to 0.1)	0.194
100 % $fT_{>MIC}$ on day 1	55 (97)	37 (70)	27 (−0.4 to −0.1)	**<0.001**
50 % $fT_{>MIC}$ on day 3	56 (98)	49 (93)	5 (−0.2 to 0.1)	0.194
100 % $fT_{>MIC}$ on day 3	55 (97)	36 (68)	29 (−0.4 to −0.1)	**<0.001**
ICU-free days	20 (12–23)	17 (0–24)	3 (−3 to 9)	0.378
ICU survivors[h]	21 (19–23)	21 (14–24)	0 (−3 to 3)	0.824
Ventilator-free days	22 (0–24)	14 (0–24)	8 (−2 to 18)	**0.043**
ICU survivors[i]	23 (21–25)	21 (0–25)	2 (−3 to 7)	0.076
14-day survival, n (%)	56 (80)	50 (71)	9 (−0.2 to 0.1)	0.237
30-day survival, n (%)	52 (74)	44 (63)	11 (−0.3 to 0.1)	0.145
WCC normalisation days	3 (2–7)	8 (4–15)	5 (1 to 5)	**<0.001**

Điều trị các chủng vi khuẩn giảm nhạy cảm

Kéo dài thời gian truyền với meropenem

Bệnh viện Hartford

Pharmacodynamic-based clinical pathway for empiric antibiotic choice in patients with ventilator-associated pneumonia☆

Table 1 Revised Hartford Hospital empiric dosing recommendations for cefepime and meropenem in VAP patients based on ability to achieve targeted pharmacodynamic exposures

Antibiotic	Dosing recommendations by CrCL (mL/min)			
	>50	30-49	<30	CRRT
Cefepime	2g q8h (3-h INF)	2g q12h (0.5-h INF)	1g q12h (0.5-h INF)	2g q8h (3-h INF)
Meropenem	2g q8h (3-h INF)	1g q8h (3-h INF)	1g q12h (3-h INF)	2g q8h (3-h INF)

CrCL indicates creatinine clearance calculated by Cockcroft-Gault equation; CRRT, continuous renal replacement therapy; INF, infusion duration.

Kuti JL and Nicolau DP. J Crit Care 2010; 25: 155-156

Truyền tĩnh mạch kéo dài điều trị các chủng vi khuẩn giảm nhạy cảm: khuyến cáo của SRLF/SFAR

Intensive Care Med (2015) 41:1181–1196
DOI 10.1007/s00134-015-3853-7

CONFERENCE REPORTS AND EXPERT PANEL

Cédric Bretonnière
Marc Leone
Christophe Milési
Bernard Allaouchiche

Strategies to reduce curative antibiotic therapy in intensive care units (adult and paediatric)

On the behalf of the French Intensive Care Society (Société de Réanimation de Langue Française, SRLF) and the French Society of Anaesthesia and Intensive Care (Société Française d'Anesthésie et de Réanimation, SFAR).

field 4c: how to administer

For intensive care patients with severe infections, we suggest maintaining the plasma concentrations of β-lactam antibiotics above MIC for at least 70 % of the time in order to increase success rate	2C
We suggest achieving a higher target (C_{min}/MIC >4–6)	2C
In intensive care unit patients, we recommend administering β-lactam antibiotics (cefepime, piperacillin–tazobactam, meropenem and doripenem) by intravenous infusion for 3 or 4 h to treat severe infections, especially if the identified bacteria have high MICs	1B
We suggest administering by continuous infusion antibiotics such as carbapenems (meropenem and doripenem), ceftazidime and piperacillin–tazobactam for the treatment of severe infections when there is a risk of pharmacodynamic failure (deep infection sites, major pharmacokinetic changes, high MIC)	2C
We recommend administering vancomycin by continuous infusion, after administration of a loading dose, to reach early target plasma concentrations, which are determinant for its efficacy	1B
We suggest using prolonged or continuous infusion of antibiotics to prevent the emergence of bacterial resistance, particularly with regard to certain strains (*S. aureus*, *P. aeruginosa*, *Enterobacteriaceae*)	UG

Truyền tĩnh mạch liên tục VAN

Continuous versus Intermittent Infusion of Vancomycin in Severe Staphylococcal Infections: Prospective Multicenter Randomized Study

MARC WYSOCKI,[1*] FREDERIQUE DELATOUR,[2] FRANÇOIS FAURISSON,[2] ALAIN RAUSS, YVES PEAN,[4] BENOIT MISSET,[5] FRANK THOMAS,[6] JEAN-FRANÇOIS TIMSIT,[7] THOMAS SIMILOWSKI,[8] HERVE MENTEC,[9] LAURENCE MIER,[10] DIDIER DREYFUSS,[10] AND THE STUDY GROUP†

Medico-Surgical Intensive Care Unit[1] and Microbiology,[4] Institut Mutualiste Montsouris, Medico-Surgical Intensive Care Unit, Hôpital Saint-Joseph,[5] Medico-Surgical Intensive Care Unit, Hôpital de Diaconesses,[6] INSERM U13[2] and Infectious Diseases Critical Care Unit,[7] Hôpital Bichat-Claude Bernard, and Respiratory Intensive Care Unit, Hôpital de la Pitié-Salpêtrière,[8] Paris, Medico-Surgical Intensive Care Unit, Hôpital V. Dupouy, Argenteuil,[9] and Medical Intensive Care Unit, Hôpital Louis Mourier, Colombes,[10] France

Received 28 June 2000/Returned for modification 2 January 2001/Accepted 5 June 2001

AAC 45:2460-2467, 2001

- 119 BN nặng nhiễm VK đa kháng (nhiễm trùng huyết 35%; viêm phổi 45%).
- Đánh giá tiêu chí lâm sàng và vi sinh
- Đánh giá an toàn, Dược động học, tính thuận lợi trong thực hành, giá thành
  - ➔ tiêu chí hiệu quả, an toàn: tương đương
  - ➔ nhanh chóng đạt nồng độ đích (20-25 mg/L, AUC = 480 - 600)
  - ➔ cần lấy ít mẫu máu để TDM hơn
  - ➔ giá trị AUC_{24h} ít dao động hơn
  - ➔ giá thành: giảm 23%

Trong thực hành: Does "one size" fits all?

Truyền tĩnh mạch liên tục so với đưa thuốc gián đoạn: kết quả phân tích gộp

- Theo dõi nồng độ dễ dàng hơn (có thể lấy mẫu ở bất cứ thời điểm nào)
- Tính toán AUC dễ dàng hơn (C_{ss} x 24)
- Độc tính trên thận có giảm hay không: còn tranh cãi
- Hiệu quả lâm sàng: tương đương

Hao JJ et al. Int. J. Antimicrob. Agents 2016; 47: 28-35
Hanrahan T et al. Int. J. Antimicrob. Agents 2015; 46: 249-253
Cataldo MA et al. J. Antimicrob. Chemother. 2012; 67: 17-24

Chế độ liều truyền liên tục của VAN áp dụng trong nghiên cứu tại khoa HSTC, bệnh viện Bạch mai

Bảng 1. Liều nạp

Cân nặng (kg)	Liều nạp (g)	Cách pha dung dịch truyền:
< 40	0.75	≤ 1.0g pha trong 250ml, truyền trong 60p 1.0g - 1.5g pha trong 250ml, truyền trong 90p > 1.5g pha trong 500ml, truyền trong 120p **Dung môi pha truyền**: natri clorid 0.9% hoặc glucose 5% ***Ghi chú***: Với những bệnh nhân cần hạn chế dịch, nồng độ vancomycin sau khi pha cần đảm bảo < 10mg/ml
40 – 65	1.0	
66 – 90	1.5	
> 90	2.0	

Mục tiêu: Ctrough = 20 - 30 mg/L

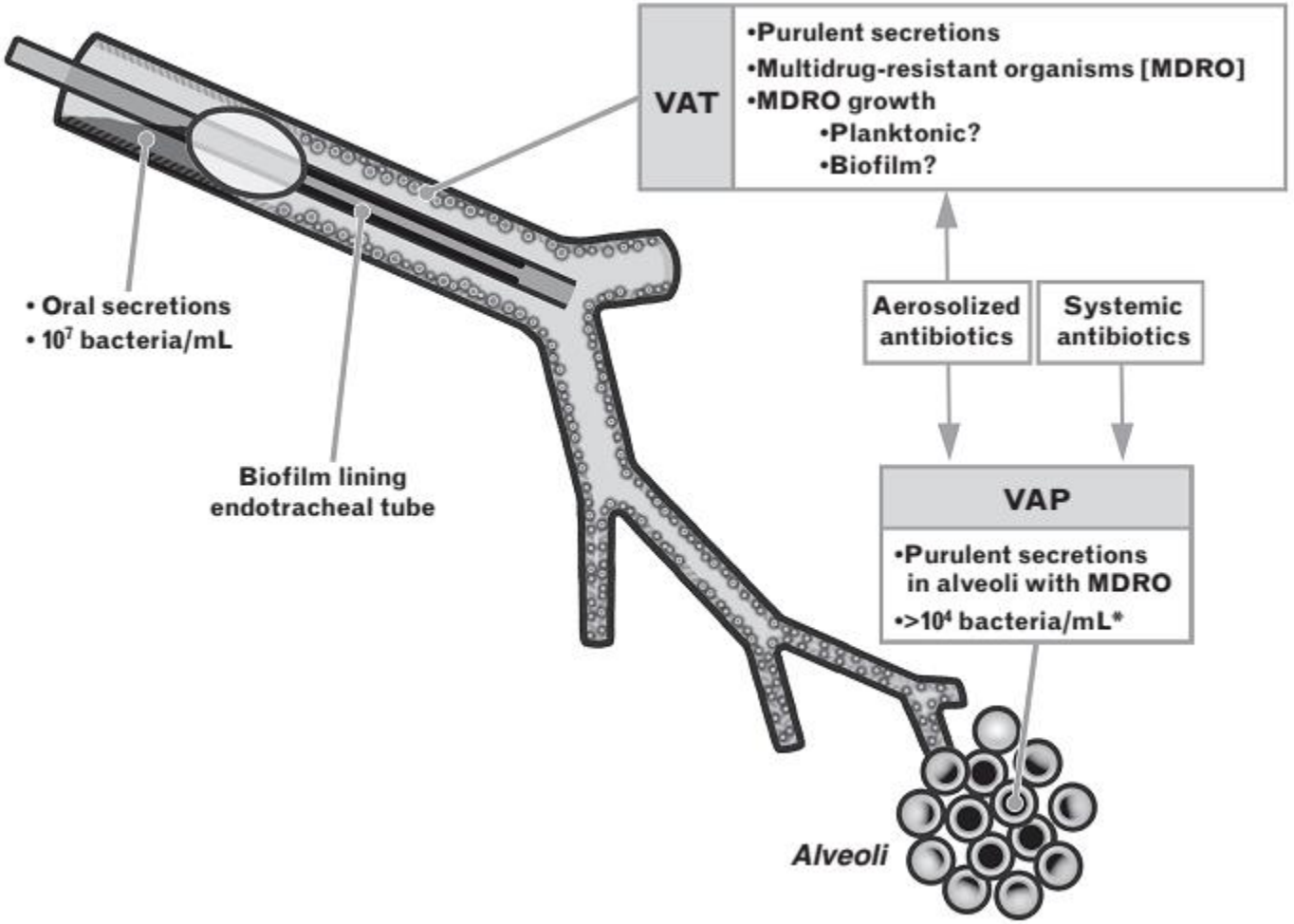
Bảng 2. Liều duy trì

Độ thanh thải creatinin* (ml/p)	Tốc độ truyền (ml/giờ)
<10	**3**
10 – 20	**5**
21 – 30	**8**
31 – 45	**10**
45 – 60	**16**
61 – 85	**21**
85 – 110	**26**
>110	**31**

Bảng 3. Hiệu chỉnh liều dùng và tốc độ truyền theo nồng độ vancomycin

Nồng độ (mg/L)	Liều dùng và tốc độ truyền cần hiệu chỉnh
0 – 5	Thêm 1 liều nạp* 20mg/kg, **và** Tăng tốc độ truyền liều duy trì thêm 20ml/h
6 – 10	Thêm 1 liều nạp* 15mg/kg, **và** Tăng tốc độ truyền liều duy trì thêm 15ml/h
11 – 15	Thêm 1 liều nạp* 10mg/kg, **và** Tăng tốc độ truyền liều duy trì thêm 10ml/h
16 – 19	Tăng tốc độ truyền liều duy trì thêm 5ml/h
20– 30	KHÔNG THAY ĐỔI
31 – 35	Giảm tốc độ truyền liều duy trì đi 5ml/h
> 35	DỪNG truyền trong 6h, **sau đó** Giảm tốc độ truyền liều duy trì đi 10ml/h

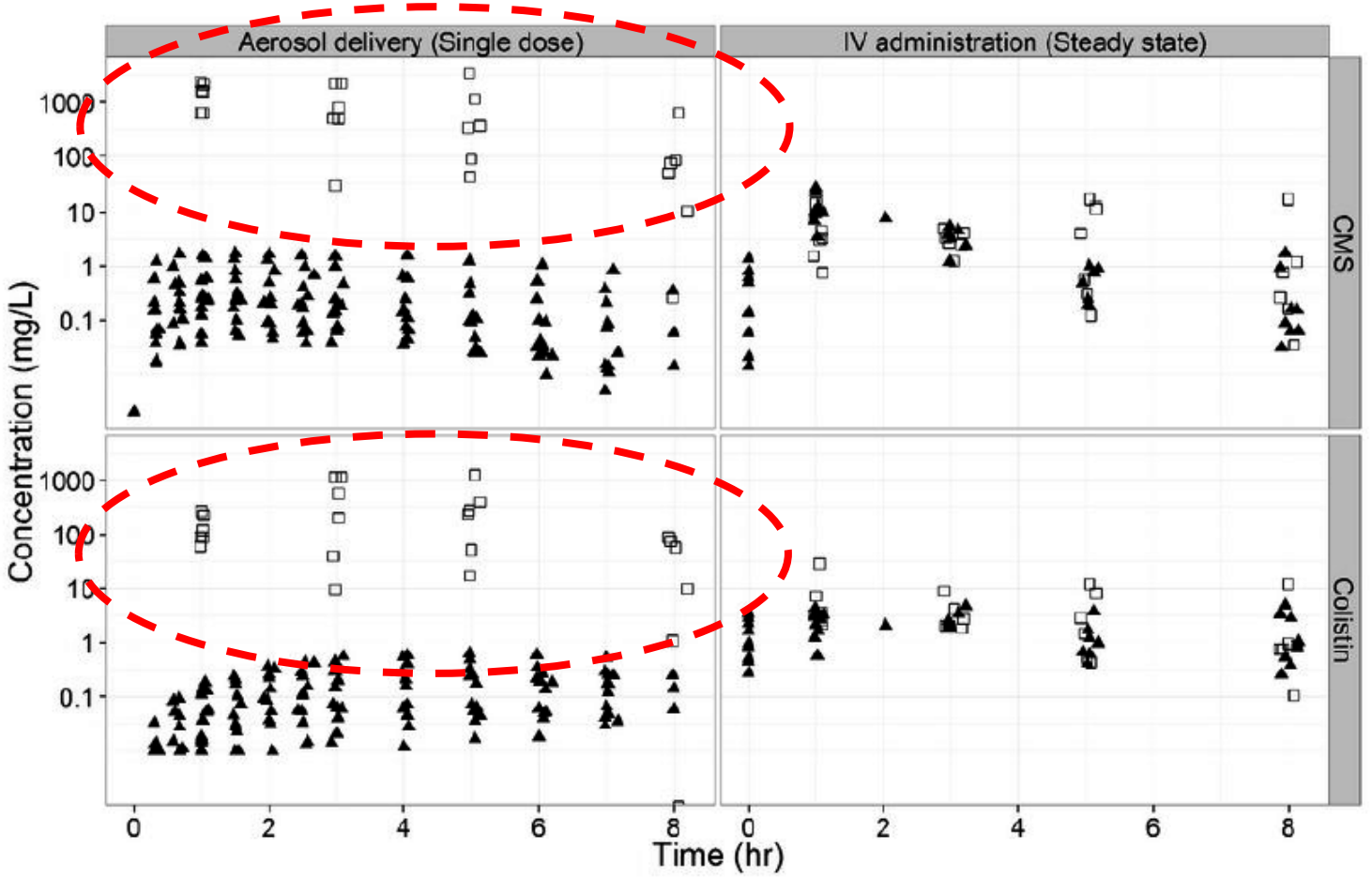
Tăng nồng độ bằng cách đưa kháng sinh đến mô đích



Palmer LB. Curr. Opin. Pulm. Med. 2015; 21: 239-249

Khí dung colistin: nghiên cứu Dược động học

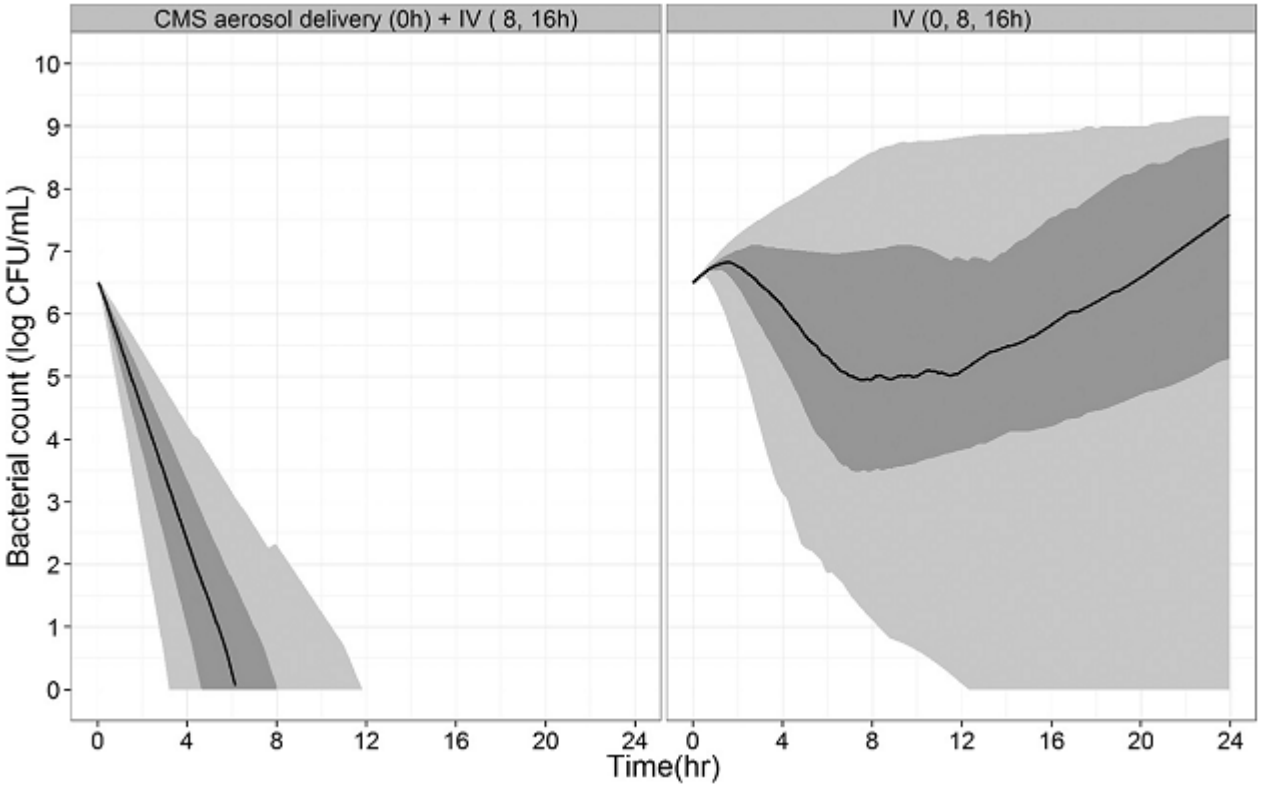
- 12 BN VAP
- Khí dung đơn liều: 2x10^6 IU (160 mg of CMS/10 ml NaCl) trong vòng 30 phút, sau đó IV: truyền 60 phút 2 x10^6 IU trong 50 ml NaCl
- So sánh nồng độ trong ELF và huyết tương



Boisson M. et al. Antimicrobiol. Agents. Chemother 2014; 58: 7331-7339.

Khí dung colistin: nghiên cứu Dược động học

- **12 BN VAP**
- **Khí dung đơn liều: 2x10^6 IU (160 mg of CMS/10 ml NaCl) trong vòng 30 phút, sau đó IV: truyền 60 phút 2 x10^6 IU trong 50 ml NaCl**
- **Ước tính tác dụng diệt khuẩn *CMS khí dung 2 MIU sau đó 2 MIU IV sau 8 h và 16 h* so với *IV 2 MIU mỗi 8 h***



Boisson M. et al. Antimicrobiol. Agents. Chemother 2014; 58: 7331-7339.

Khí dung colistin: nghiên cứu lâm sàng

The Role of Aerosolized Colistin in the Treatment of Ventilator-Associated Pneumonia: A Systematic Review and Metaanalysis*

Antonis Valachis, MD, PhD[1]; George Samonis, MD, PhD[2]; Diamantis P. Kofteridis, MD, PhD[2]

parameter	p	Odds ratio (95% CI)
Clinical response	0.006	1.57 (1.14-2.15)
Microbiological eradication	0.01	1.61 (1.11-2.35)
Infection-related mortality	0.04	0.58 (0.34-0.96)
Overall mortality	0.06	0.74 (0.54-1.01)
Nephrotoxicity	0.45	1.18 (0.76-1.83)

- **16 nghiên cứu lâm sàng, mức độ bằng chứng thấp (cohort, case-control, 1 RCT)**
- **Liều dùng khí dung thay đổi**
- **Không bao giờ dùng khí dung đơn độc**

Crit. Care. Med 2015; 43: 527-533

Clinical Infectious Diseases

IDSA GUIDELINE

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

ROLE OF INHALED ANTIBIOTIC THERAPY

XIV. Should Patients With VAP Due to Gram-Negative Bacilli Be Treated With a Combination of Inhaled and Systemic Antibiotics, or Systemic Antibiotics Alone?

Recommendation

1. For patients with VAP due to gram-negative bacilli that are susceptible to only aminoglycosides or polymyxins (colistin or polymyxin B), we suggest both inhaled and systemic antibiotics, rather than systemic antibiotics alone *(weak recommendation, very low-quality evidence)*.

Vai trò của TDM khi sử dụng vancomycin

OPEN ACCESS Freely available online

PLOS ONE

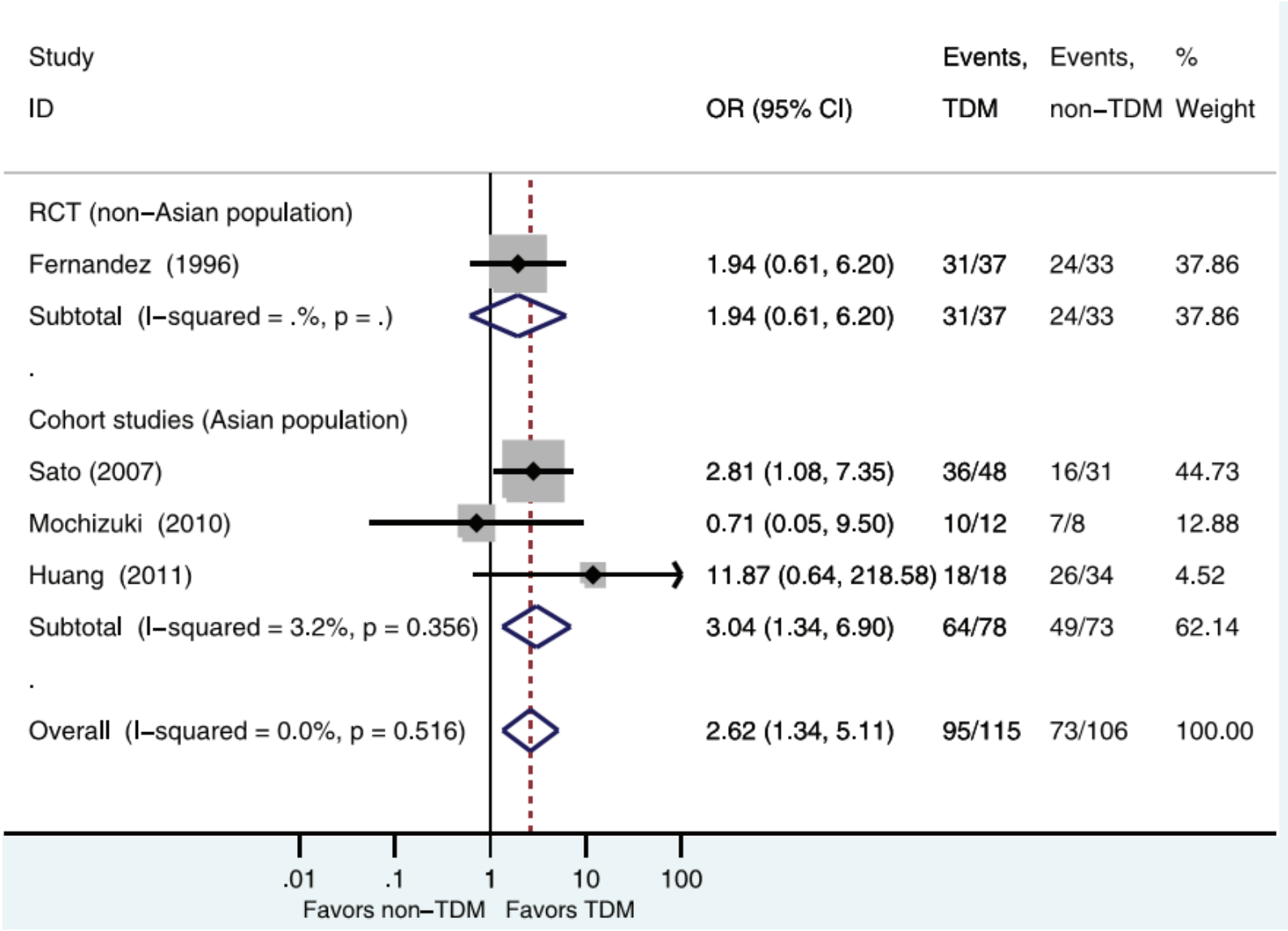
Benefits of Therapeutic Drug Monitoring of Vancomycin: A Systematic Review and Meta-Analysis

Zhi-Kang Ye[1,2], Hui-Lin Tang[1], Suo-Di Zhai[1]*

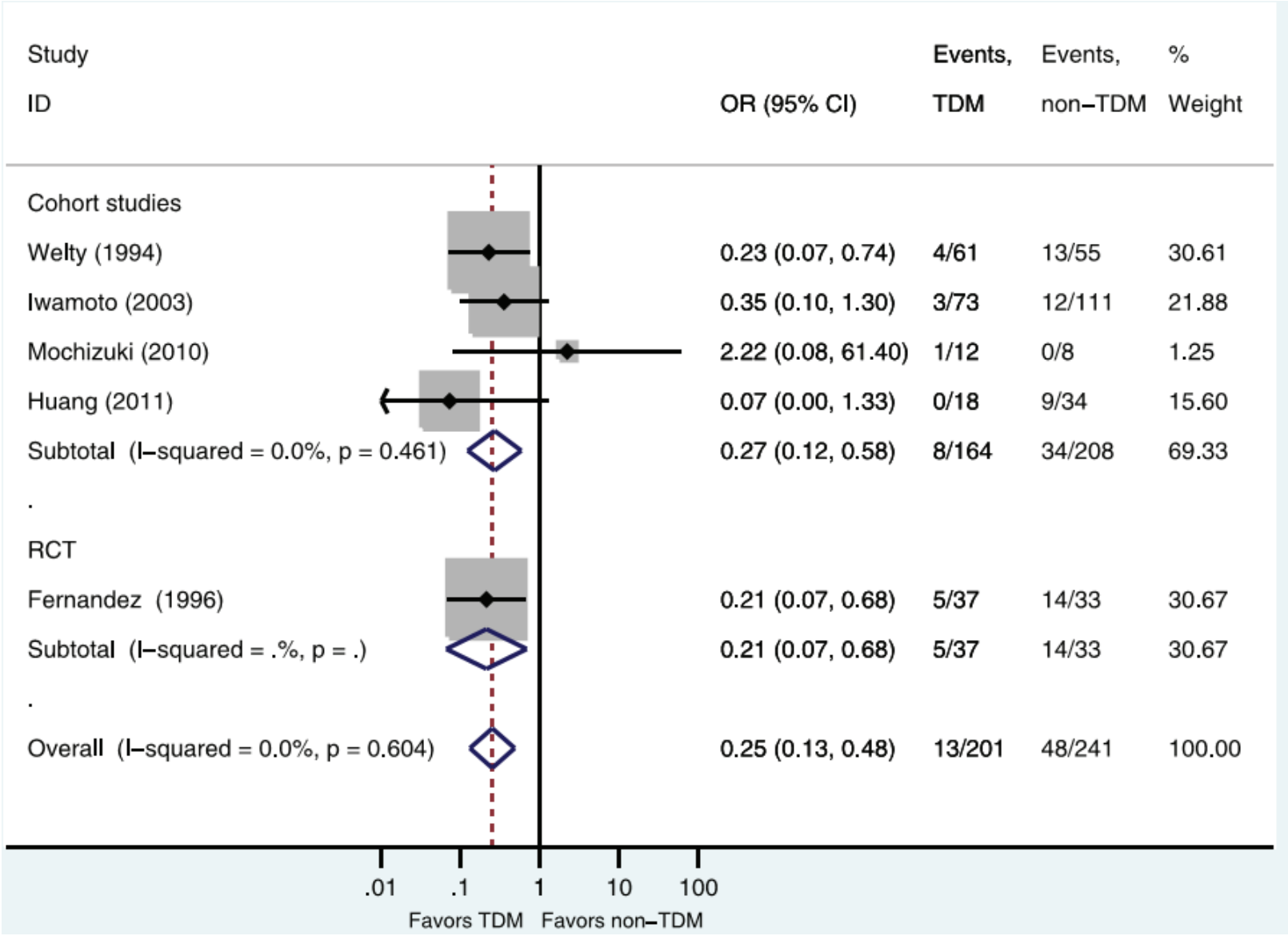
1 Department of Pharmacy, Peking University Third Hospital, Beijing, China, **2** Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University Health Science Center, Beijing, China

2013

Vai trò của TDM khi sử dụng vancomycin: hiệu quả lâm sàng



Vai trò của TDM khi sử dụng vancomycin: độc tính trên thận



Giám sát điều trị thông qua nồng độ thuốc trong máu (TDM)

International Journal of Antimicrobial Agents 36 (2010) 332–339

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Therapeutic drug monitoring of β-lactams in critically ill patients: proof of concept

Jason A. Roberts[a,b,c,*], Marta Ulldemolins[a,d], Michael S. Roberts[e,f], Brett McWhinney[g], Jacobus Ungerer[g], David L. Paterson[h,i], Jeffrey Lipman[a,c]

Giám sát điều trị thông qua nồng độ thuốc trong máu (TDM)

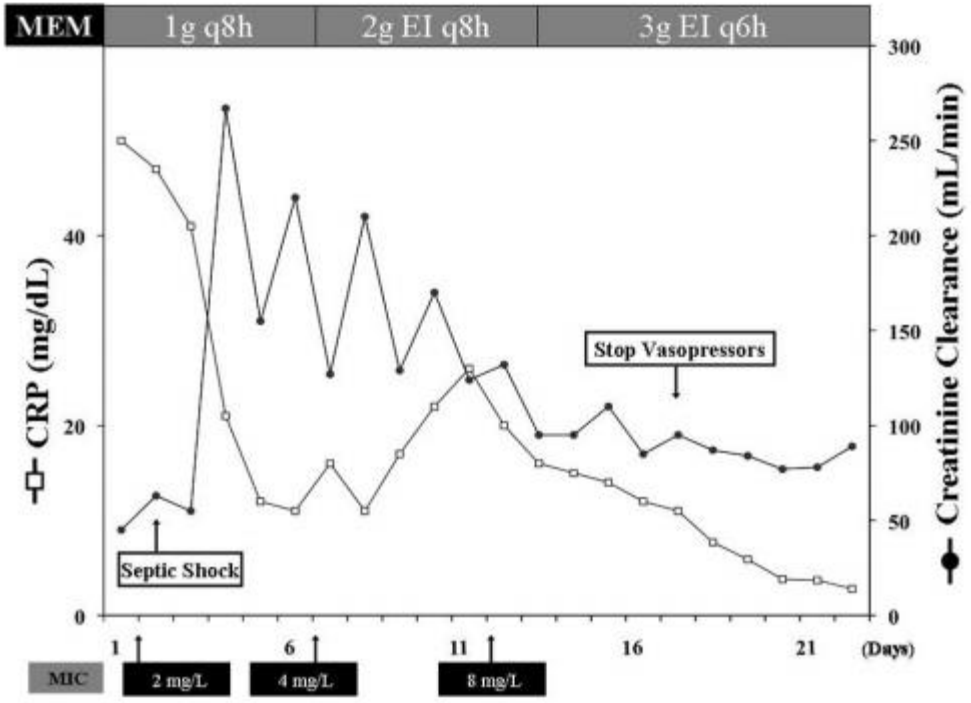
Optimal Meropenem Concentrations To Treat Multidrug-Resistant *Pseudomonas aeruginosa* Septic Shock

Fabio Silvio Taccone,[a] Frédéric Cotton,[b] Sandrine Roisin,[c] Jean-Louis Vincent,[a] and Frédérique Jacobs[d]

Department of Intensive Care, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium[a]; Department of Clinical Biology, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium[b]; Department of Microbiology, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium[c]; and Department of Infectious Diseases, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium[d]

Day of therapy	MEM dose	Time of sampling	MEM concn (mg/liter)	MIC (mg/liter)	% T > 4× MIC
1	1 g q8h				
2	1 g q8h	2 h	12.3	2	37
		8 h	<2.0		
5	1 g q8h	2 h	13.4	2	39
		8 h	<2.0		
9	2 g EI q8h	3 h	17	4	39
		8 h	3		
15	3 g EI q6h	3 h	43	8	51
		6 h	19		

[a] MEM, meropenem; q8h and q6h, every 8 h and 6 h; EI, extended infusion (over period); 2 h, 3 h, 6 h, and 8 h, 2, 3, 6, and 8 h after the onset of MEM administrati
T > 4× MIC, time above 4 times the MIC.




COMBAT
DRUG RESISTANCE
NO COMMITMENT
WEAK SURVEILLANCE
POOR DRUG QUALITY
IRRATIONAL DRUG USE
NO INFECTION CONTROL
LACK OF RESEARCH
DRUG RESISTANCE
No action today, no cure tomorrow
7 APRIL 2011 WORLD HEALTH DAY
World Health Organization