The Efficacy of Doripenem in Intra-abdominal Infection

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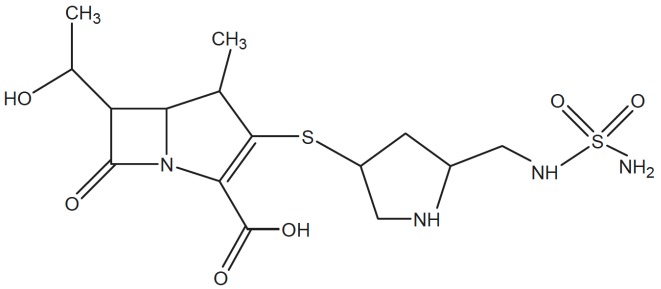
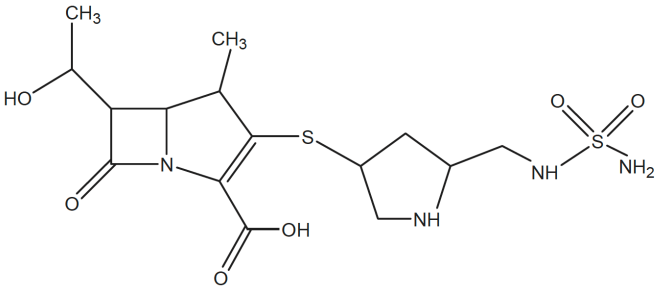
Doripenem



- DORIPENEM
  - Indikasi: complicated intra-abdominal infections dan UTIs, termasuk pyelonephritis.
  - C max: 8,1-63 mg/L
  - AUC: 8,7-75,6 mcg jam/mL
  - Ikatan obat-protein: minimal ($\pm 8{,}1\%$)
  - Vd: 16,8 L
  - Ekskresi: Renal (10,8 L/jam: 15% melalui Glomerulus dan tubulus, 70% diekskresi dalam bentuk tidak berubah)

Doripenem



- DORIPENEM
  - Time-dependent bactericidal effects
  - Penelitan → prolonging infusion time (4 jam) lebih efektif meningkatkan farmakokinetik dan farmakodinamik (T>MIC)
  - Memiliki sulfamoly-aminomethyl-pyrrolidinylthio side chain → meningkatkan potensi melawan Gram-positive bacteria.

IDSA Guideline

- Prinsip: enteric aerobic gram negatif, facultative bacilli, enteric streptococci gram positif

Table 2. Agents and Regimens that May Be Used for the Initial Empiric Treatment of Extra-biliary Complicated Intra-abdominal Infection

Regimen	Community-acquired infection in pediatric patients	Community-acquired infection in adults	
		Mild-to-moderate severity: perforated or abscessed appendicitis and other infections of mild-to-moderate severity	High risk or severity: severe physiologic disturbance, advanced age, or immunocompromised state
Single agent	Ertapenem, meropenem, imipenem-cilastatin, ticarcillin-clavulanate, and piperacillin-tazobactam	Cefoxitin, ertapenem, moxifloxacin, tigecycline, and ticarcillin-clavulanic acid	Imipenem-cilastatin, meropenem, doripenem, and piperacillin-tazobactam
Combination	Ceftriaxone, cefotaxime, cefepime, or ceftazidime, each in combination with metronidazole; gentamicin or tobramycin, each in combination with metronidazole or clindamycin, and with or without ampicillin	Cefazolin, cefuroxime, ceftriaxone, cefotaxime, ciprofloxacin, or levofloxacin, each in combination with metronidazole[a]	Cefepime, ceftazidime, ciprofloxacin, or levofloxacin, each in combination with metronidazole[a]

[a] Because of increasing resistance of *Escherichia coli* to fluoroquinolones, local population susceptibility profiles and, if available, isolate susceptibility should be reviewed.

SIS guideline

- Prinsip umum penatalaksanaan:
  - Aktivitas melawan bakteri aerob gram negatif: Enterobacteriaceae, Streptococci, obligate enteric anaerob

Empiric antimicrobial therapy

TABLE 9. RECOMMENDED EMPIRIC ANTIMICROBIAL REGIMENS FOR PATIENTS WITH COMMUNITY-ACQUIRED INTRA-ABDOMINAL INFECTION

Lower-risk patients[a,b]	*Higher-risk patients*
Single agents	
Ertapenem	Piperacillin-tazobactam
Moxifloxacin[c]	Doripenem[f]
	Imipenem-cilastatin
	Meropenem[f]
Combination regimens	
Cefotaxime or ceftriaxone plus metronidazole[d]	Cefepime plus metronidazole[f,g]
Ciprofloxacin plus metronidazole[c,e]	Aztreonam plus metronidazole plus vancomycin[h]

- Lower risk:
  - Prinsipnya menghindari broad spectrum termasuk anti fungal → agent yang dipilih tidak terlalu efektif dalam melawan Pseudomonas spp. atau Enterococcus spp.
- Higher risk:
  - Prinsipnya broader-spectrum empiric antimicrobial agents

WSES guideline

Table 4 Antibiotics for treating patients with IAIs based upon susceptibility [253]

Antibiotic	Enterococci	Ampicillin-resistant enterococci	Vancomycin-resistantenterococci	*Enterobacteriaceae*	ESBL-producing *Enterobactericeae*	*Pseudomonas aeruginosa*	Anaerobic gram-negative bacilli
Penicillins/beta-lactamase inhibitors							
Amoxicillin/clavulanate	+	–	–	+	–	–	+
Ampicillin/sulbactam	+	–	–	+	–	–	+/–
Piperacillin/tazobactam	+	–	–	+	+/–	+	+
Carbapenems							
Ertapenem	–	–	–	+	+	–	+
Imipenem/cilastatin	+/–[a]	–	–	+	+	+	+
Meropenem	–	–	–	+	+	+	+
Doripenem	–	–	–	+	+	+	+

Duration of treatment cIAI

- IDSA (2010)
  4-7 days
- SIS (2017)
  - 4 days with source-control procedure
  - 5-7 days in established IAI and no source-control procedure
- WSES (2017)
  - 3-5 days with adequate sources-control procedure
  - 5-7 days for uncontrolled infection or tx failure

EVIDENCES

1 penelitian pada fase III di Eropa dan Amerika

- Subject:
  - Px usia ≥ 18 tahun dan
  - Terdiagnosis: cIAI (cholecystitis with rupture/perforation/progression of infection beyond gallbladder wall, diventricular disease, appendiceal perforation, acute gastric and duodenal perforation, traumatic intestinal perforation, peritonitis, intra-abdominal abscess), menjalani operasi dalam 24 jam
- Intervensi:
  - Doripenem 500 mg tiap 8 jam lama infus minimal 1 jam;
  - Meropenem 1 g tiap 8 jam IV bolus 3-5 menit
  - Setelah 3 hari terapi, diganti menjadi oral amox/clav apabila ada perbaikan kondisi dari lab dan gejala

- Total 476 pasien (237 Doripemem, 239 Meropenem)
- Clinical evaluable mencapai TOC:
  - 85,9% Doripenem;
  - 85,3% Meropenem
  - treatment different 0,6%, 95% CI -7,7% sampai 9,0% → Doripenem noninferior dibandingkan Meropenem
- Clinical cure rate:
  - 77,9% Doripenem;
  - 78,9% Meropenem
  - treatment different 1,0% (95%CI -9,7%-7,7%) → Doripenem noninferior dibandingkan Meropenem, not significantly different

...cont.

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

*Favorable microbiological outcome with doripenem minus cure rate with meropenem; not significantly different. These analyses were done for isolates with the number of qualifying intra-abdominal baseline pathogens in the microbiologically evaluable population of ≥10 in the doripenem arm.

...cont.

Table VI. Tolerability overview in patients who received IV doripenem or meropenem for complicated intra-abdominal infection (intent-to-treat population). Values are no. (%) of patients.

Parameter	Doripenem (n = 235)	Meropenem (n = 236)
Patients with AEs	195 (83.0)	184 (78.0)
Patients with study drug-related AEs	76 (32.3)	63 (26.7)
Patients with SAEs	31 (13.2)	33 (14.0)
Patients with study drug-related SAEs	0	0
Discontinuations due to AEs	12 (5.1)	5 (2.1)
Discontinuations due to study drug–related AEs	5 (2.1)	3 (1.3)
Deaths	5 (2.1)	7 (3.0)

AEs = adverse events; SAEs = serious AEs.

Table VII. Drug-related adverse events (AEs)* in patients who received IV doripenem or meropenem for complicated intra-abdominal infection (intent-to-treat population). Values are no. (%) patients.

AE	Doripenem (n = 235)	Meropenem (n = 236)
Nausea	16 (6.8)	3 (1.3)
Diarrhea	15 (6.4)	11 (4.7)
Phlebitis	8 (3.4)	5 (2.1)
Vomiting	6 (2.6)	6 (2.5)
Rash	6 (2.6)	0
Headache	5 (2.1)	3 (1.3)
Anemia	5 (2.1)	1 (0.4)
Oral candidiasis	4 (1.7)	6 (2.5)
Pyrexia	4 (1.7)	5 (2.1)
Hepatic enzyme increase	2 (0.9)	6 (2.5)
Urinary tract fungal infection	2 (0.9)	5 (2.1)

*Occurring in ≥2% of patients in either treatment arm.

- Durasi terapi: 6,8 hari Doripenem; 6,6 hari Meropenem → not signinficantly different
- ADR: 83% Doripenem; 78% Meropenem → not significantly different
  - Common AEs: nausea, pyrexia, diarrhea, anemia, phlebitis

1 prospective, multicenter, double blind trial

- Sample: total 486 px, random Doripenem 500 mg tiap 8 jam vs Meropenem 1g tiap 8 jam
- Hasil:
  - Doripenem non-inferior pada clinical cure rate dan clinical cure rate
  - Most common ADR: similar with Phase III trial

1 Systematic review and meta-analysis, 8 RCT

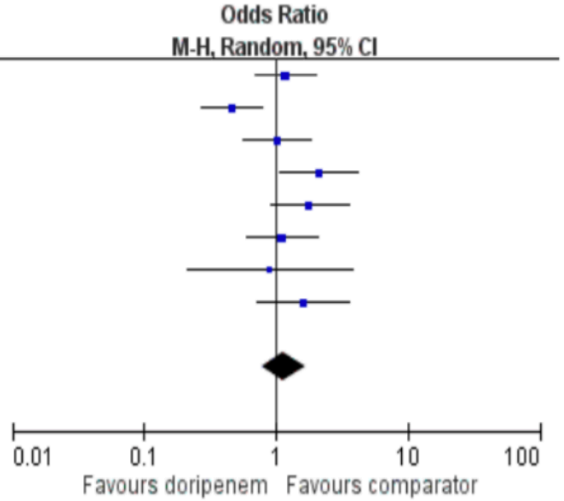
- Sample: n=1736 px dg Doripenem 500 mg tiap 8 jam atau 1 g tiap 8 jam vs n=1763 px dengan Others antibiotics
  - Other antibiotics: Piperacillin/tazobactam 4,5 g tiap 6 jam; Meropenem 1 g tiap 8 jam; Imipenem/cilastatin 500 mg tiap 6 jam dan 1 g tiap 8 jam; Levofloxacin 250 mg qd; Ceftazidime/avibactam 2 g/500 mg tiap 8 jam

- **Hasil**:
  - Clinical success: overall: similar clinical success with comparators (OR, 1,15; 95% CI, 0,79-1,66 I^2=58%)
  - Disease group:
    - UTI: OR, 1,89; 95% CI, 1,13-3,17, I^2=0%
    - IAI: OR, 1,00; 95% CI, 0,57-1,72
    - Pneumonia: OR, 0,84; 95% CI, 0,46-1,53, I^2=72%
  - Treatment group:
    - Doripenem vs Imipenem: no different (OR, 0,76; 95% CI, 0,38-1,55, I^2=66%)
    - Doripenem vs Meropenem: similar (OR, 1,31; 95% CI, 0,75-2,28, I^2=34%)

Study or Subgroup	Doripenem Events	Total	Comparator Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Chastre et al, 2008	86	126	79	122	15.4%	1.17 [0.69, 1.98]
Kollef et al, 2012	47	115	67	112	15.4%	0.46 [0.27, 0.79]
Lucasti et al, 2008	163	188	161	186	14.2%	1.01 [0.56, 1.84]
Naber et al, 2009	272	286	240	266	12.9%	2.10 [1.07, 4.12]
Oyake et al, 2019	39	65	31	68	12.6%	1.79 [0.90, 3.56]
Rea-Neto et al, 2008	109	134	95	119	13.7%	1.10 [0.59, 2.06]
Tazuma et al, 2015	54	58	60	64	5.1%	0.90 [0.21, 3.78]
Wagenlehner et al, 2016	407	417	378	393	10.8%	1.62 [0.72, 3.64]
Total (95% CI)		**1389**		**1330**	**100.0%**	**1.15 [0.79, 1.66]**
Total events	1177		1111			

Heterogeneity: $Tau^2 = 0.16$; $Chi^2 = 16.73$, $df = 7$ ($P = 0.02$); $I^2 = 58\%$

Test for overall effect: $Z = 0.73$ ($P = 0.47$)



- Adverse events
  - Similar risk with other antibiotics (OR, 0,98; 95% CI, 0,83-1,17, I2=33%)
  - Nausea, diare, konstipasi, headache

Penelitian terkait profil farmakodinamik di Asia-Pasifik (New Zealand, Philipines, Singapore, Thailand, Vietnam)

Antibiotics:

- Doripenem
- Meropenem
- Imipenem

Isolat:

- *E. coli* (n=238)
- *K. pneumoniae* (n=187)
- *P. aeruginosa* (n=625)
- *A. baumanii* (n=115)

Disease

- Complicated Intra-abdominal infection
- Blood stream infection/nosocomial pneumonia

Secara umum

...cont.

- Aktivitas farmakodinamik Doripenem terhadap *P. aeruginosa* dibandingkan dengan Meropenem dan Imipenem
- MIC_{50} dan MIC_{90}:
  - Dor & Mer: similar, kecuali pada *P. aeruginosa*
  - Imi: higher, kecuali pada *A. baumanii*

	MIC_{50} (mg/L)	MIC_{90} (mg/L)	Susceptibility (%)[a]
Total isolates			
E. coli (*n* = 238)			
Doripenem	0.032	0.06	100
Imipenem	0.25	0.5	98
Meropenem	0.032	0.06	100
K. pneumoniae (*n* = 187)			
Doripenem	0.032	0.125	99
Imipenem	0.25	0.5	99
Meropenem	0.032	0.125	99
P. aeruginosa (*n* = 625)			
Doripenem	0.5	8	75
Imipenem	2	32	67
Meropenem	0.5	16	72
A. baumannii (*n* = 115)			
Doripenem	32	≥64	27
Imipenem	32	≥64	29
Meropenem	32	≥64	27

Secara umum

- Susceptibility:
  - Semua carbapenem susceptible ≥ 98% pada *E. coli* dan *K. pneumoniae*
  - 67%-75% susceptible terhadap *P. aeruginosa*
  - < 30% susceptible terhadap *A. baumanii*

	Doripenem	Meropenem	Imipenem
Enterobacteriaceae	MIC ≤ 1 mg/L		
P. aeruginosa	MIC ≤ 2 mg/L		
A. baumanii	MIC 1 mg/L	MIC 4 mg/L	

Dosis atau kecepatan infus

...cont.

- Semua carbapenem mencapai efek optimal pada *E. coli* dan *K. pneumoniae*
- *P. aeruginosa*: efek optimal dicapai pada antibiotik:
  - Doripenem 1000 mg tiap 8 jam dengan pemberian infus selama 4 jam
  - Doripenem 2000 mg tiap 8 jam dengan pemberian infus selama 1 jam dan 4 jam
  - Meropenem 2000 mg tiap 8 jam dengan pemberian infus selama 3 jam
- Tidak ada yg mencapai efek optimal pada isolat *A. baumanii*

Countries

...cont.

- *P. aeruginosa*
  - Susceptibility rates highest with Doripenem
  - Efek paling optimal dicapai pada pemberian Doripenem 1000 mg dan 2000 mg tiap 8 jam dengan lama infus 1 jam dan 4 jam.

Susceptibility rates (%) of carbapenems against *Pseudomonas aeruginosa* in participating countries.[a]

	New Zealand ($n = 29$)	Philippines ($n = 90$)	Singapore ($n = 120$)	Thailand ($n = 296$)	Vietnam ($n = 90$)
Doripenem	100	77	82	75	58
Imipenem	79	59	78	70	52
Meropenem	93	72	78	71	56

[a] Susceptibility rates were calculated using the Clinical and Laboratory Standards Institute (CLSI) breakpoints of MIC ≤ 2 mg/L for all of the carbapenems.

In vitro study

400 isolate *A. baumanii*, control test using *E. coli* & *P. aeruginosa*. MIC using E-strips

- 97,8% resistant to Doripenem, Imipenem, and Meropenem
- MIC_{50} Doripenem similar to Meropenem
- Susceptibility to Doripenem: 3 isolates (MIC 0,125-1 $\mu g/mL$)

Table 1 Susceptibility rate of *Acinetobacter baumannii* isolates to carbapenems, MICs, error rates and categorical agreement for susceptibility to carbapenems by disc diffusion and *E*-test

	Disc diffusion (n = 400)			*E*-test (n = 200)					No (%) of errors							
Antibiotic	Susceptible n (%)	Intermediate	Resistant	MIC_{50} ($\mu g\ ml^{-1}$)	MIC_{90} ($\mu g\ ml^{-1}$)	Range	Mode	% S/I/R	Minor n (%)	Major	Very major	% Categorical agreement	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Doripenem	8 (2)	1 (0·3)	391 (97·8)	32	>32	0·125–>32	>32	1·5/2/96·5	5 (2·5)	0 (0)	0 (0)	97·5	100	66·7	99·5	100
Imipenem	6 (1·5)	3 (0·8)	391 (97·8)	>32	>32	0·25–>32	>32	1/0·5/98·5	2 (1)	0 (0)	0 (0)	99	100	50	99·5	100
Meropenem	9 (2·3)	0 (0)	391 (97·8)	32	>32	0·19–>32	>32	1·5/0/98·5	0 (0)	0 (0)	0 (0)	100	100	100	100	100

S, susceptible; I, intermediate; R, resistant; PPV, positive predictive value; NPV, negative predictive value.

- Doripenem menghambat *A. baumanii* lebih banyak dibandingkan dengan karbapenem lain

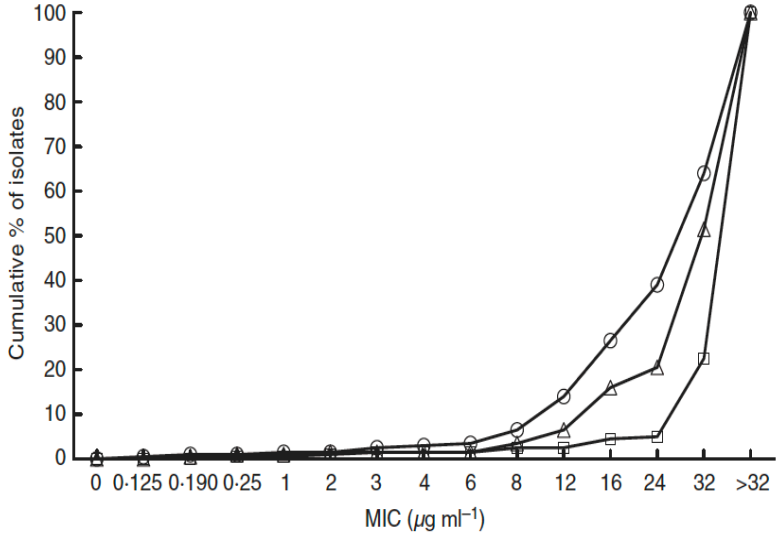


Figure 2 Cumulative percentage of minimum inhibitory concentration (MIC) distributions of carbapenems against *Acinetobacter baumannii* (n = 200). (○) doripenem, (□) imipenem and (△) meropenem.

HARGA

	Meropenem	Doripenem
Generik 500 mg	86.800	334.060
Generik 1 g	128.400	-
Paten 500 mg	226.180-287.100	394.500-665.500
Paten 1 g	418.450-722.800	-

Kesimpulan

- Doripenem memiliki aktivitas farmakodinamik yang mirip dengan Meropenem
- Doripenem memiliki aktivitas farmakodinamik yang sedikit lebih baik dibandingkan Imipenem
- Efficacy dan safety dari penggunaan Doripenem tidak berbeda bermakna dibandingkan dengan Meropenem

Thanks!

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MEROPENEM

- T ½ : 1 jam
- Vd: 0,25 L/kg
- C max: 23, 49, 115 microgram/mL
- Binding protein: 2 %
- Eliminasi: 70% melalui ginjal,