Efficacy of Colistin in combination with Carbapenem and Tigecycline in patients with pneumonia caused by multidrug-resistant *Acinetobacter baumannii*

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Clinical Microbiology Conference 2017
Bangkok, 03-04 July 2017

Background

- Acinetobacter baumannii is a Gram-negative, aerobic and commonly found in hospital setting.
- Often causes problem in ICU setting
- Intrinsically Multidrug-resistance

Gootz TD, Marra A. Acinetobacter baumannii : an emerging multidrug-resistant threat. Expert Rev Anti Infect Ther. 2008;6:309–25.

Background (2)

The continuous presence of *Acinetobacter baumannii* in clinical specimens from hospitalized patients

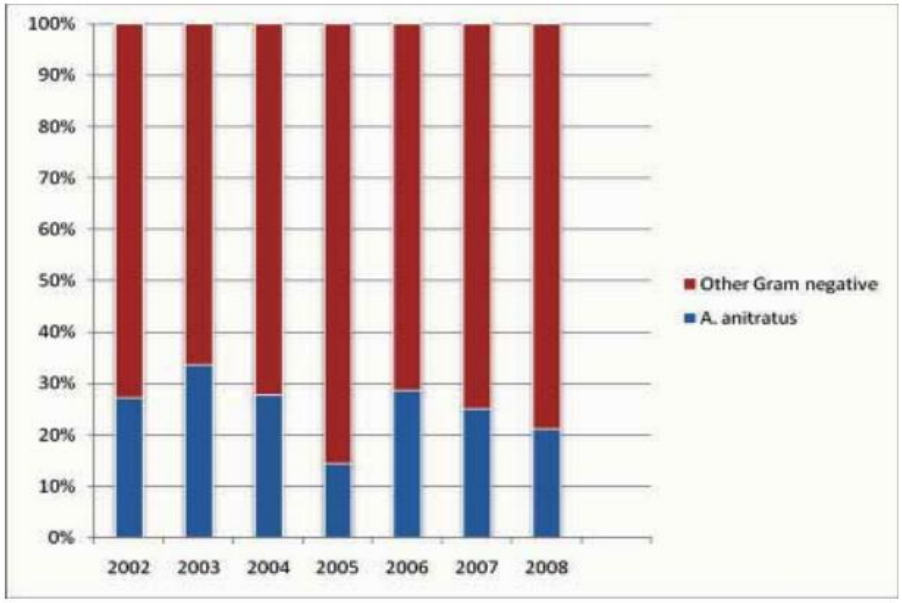


Figure 1. Percentage of isolated Acinetobacter anitratus compared to other Gram negative bacteria

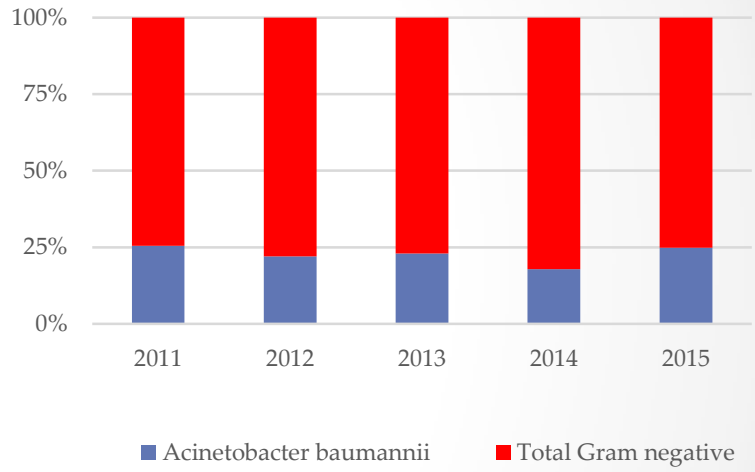


Figure 1
Lucky H Moehario and Enty Tjoa.
Isolation of environmental microorganisms from clinical specimens: A report of the occurrence of *Acinetobacter anitratus* in bloodstream from hospitalized patients in Jakarta in 7 year periods from 2002 to 2008**. Medical Journal of Indonesia, 2009; 18 (4): 227-232**

Figure 2. Percentage of *Acinetobacter baumannii* (n=224) compared to Other Gram negative bacteria (n=776), isolated from sputum and BAL in a private hospital, West Jakarta, 2011-2015.

[Unpublished data]

Background (3)

The treatment has become difficult

- Treatment against multidrug-resistant Acinetobacter baumannii (MDRAB) has now become a challenge.
- Carbapenem, Colistin, Tigecycline, Sulbactam, Rifampicin, Minocycline in the form of combination are considered for treating MDRAB
- Combination therapy may be more useful than monotherapy in treatment of MDR/XDRAB pneumonia.

Objective

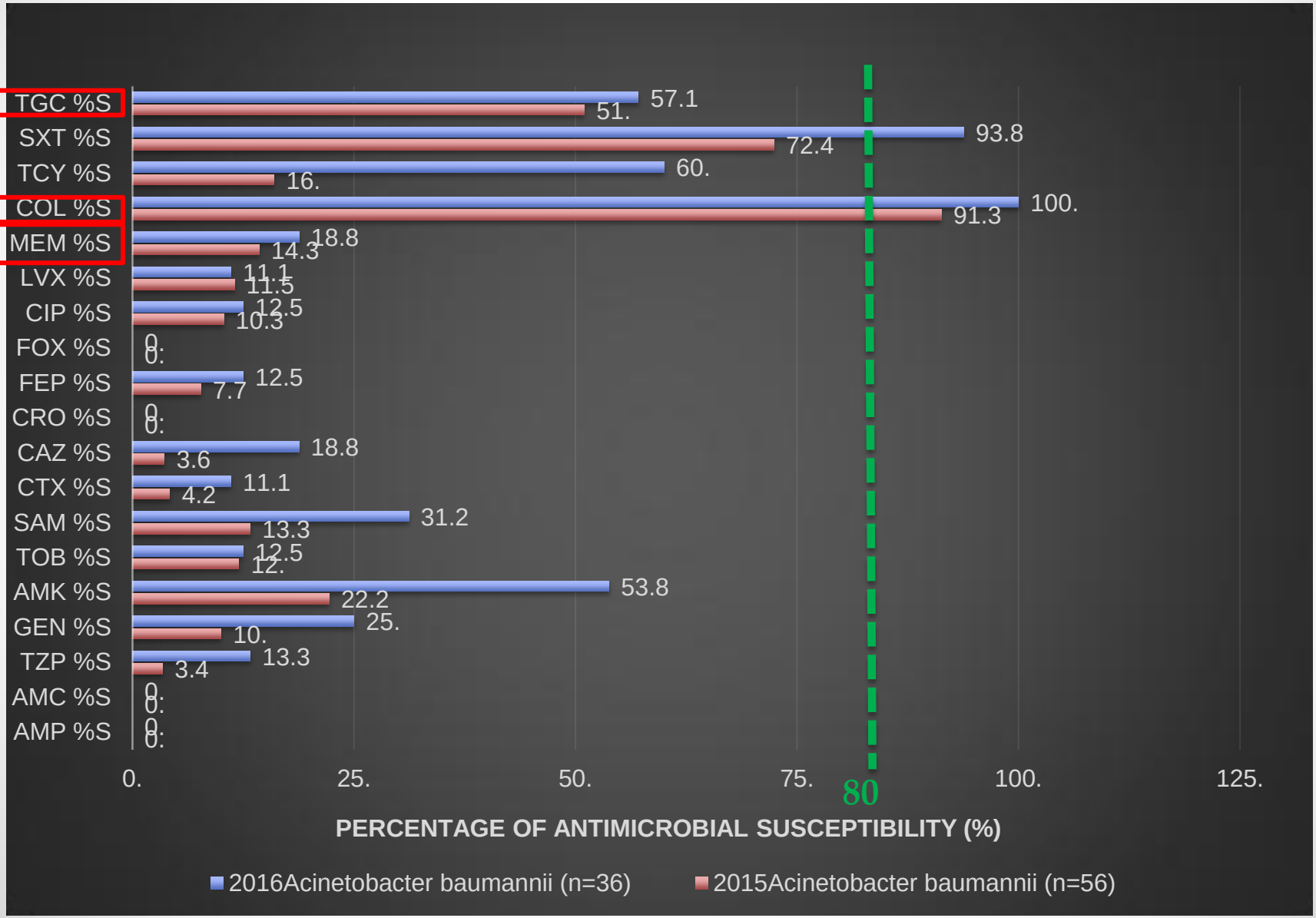
- To assess the efficacy of Colistin based combination

Colistin in combination with Carbapenem

Colistin in combination with Tigecycline

in patients with pneumonia with *Acinetobacter baumannii* isolated from specimens from low respiratory tract

Susceptibility pattern of *Acinetobacter baumannii* from ICU, Private hospital, Jakarta, Indonesia, *2015-2016*



Methods

- This is a retrospective and observational study
- Conducted in a private hospital in Jakarta, Indonesia (150 bed)
- MDRAB were isolated from specimen of lower respiratory tract from patients with pneumonia in intensive care unit (ICU) during 4 year period (2011-2015)

Methods (2)

- Clinical parameters:
  - Blood leukocyte,
  - Differential count,
  - Body temperature,
  - Pro calcitonin,

- The analysis of studied clinical parameters were performed before and after drug administration
  - 1-3 day before and 2-5 days after drug administration

Methods (3)

Microbiological work up

- Isolation : Blood agar, Mac Conkey agar
- Identification and Antimicrobial Susceptibility Test : Vitek 2 (Biomeriuex®)
- Antimicrobial Susceptibility Test for Carbapenem and Tigecycline : Vitek 2 (Biomeriuex®)
- Antimicrobial Susceptibility Test for Colistin : Disc Susceptibility Testing (Kirby Bauer Method)

  Colistin disc 10µg

  resistant ≤10 mm; susceptible ≥ 14 mm, [Gales et al]

- Data collection: WHO-NET 5.6

Samples

Inclusion criteria

- Specimens: sputum* or BAL and revealed MDR Acinetobacter baumannii

  * with >= 25 leucocyte ‘ LPF and < 10 /LPF of squamous ephitelial cells

- Studied antibiotics treatment : Colistin plus Carbapenem/Tigecycline was given > 1 day
  - Dose of Carbapenem : 3 x 1-1.5 g
  - Dose of Colistin 3 x 1,500,000 unit IV
  - Dose of Tigecycline 2 x 50 mg IV (loading dose 100mg)

Exclusion

- Studied laboratory results on relevant period was incomplete**

  **Lack of < 2 parameters result still accepted

Result

- Sixty eight MDRAB were found from various specimens
- Fifty nine patients with MDRAB pneumoniae were studied

- Colistin-Carbapenem combination therapy was used in 11 patients (15 cases period)
- Colistin-Tigecycline combination was administered in 9 patients (11 cases period)
- Other (37) were administered with antibiotics other than regimen studied

Patients characteristic with positive culture of *Acinetobacter baumannii* (n=59)

Characteristic		n	Percentage
Age	Median	66	-
	Average	60,2	-
	<21 year	5	8,5 %
	21-40 year	5	8,5 %
	41-60 year	15	25,4 %
	61-80 year	22	37,3 %
	>80 year	12	20,3 %
Gender	Male	30	50,8 %
	Female	29	49,2 %
Specimen type	Sputum	53	77,9 %
	BAL	4	5,9 %
	Blood	6	8,8 %
	Pus	2	2,9 %
	Throat swab	1	1,5 %
	Feces	1	1,5 %
	Pleural fluid	1	1,5 %
Ward	ICU	36	61 %
	IMC	10	16,9 %
	General ward	13	22,1 %

Efficacy of **Colistin plus Carbapenem** to several inflammatory parameters (n=15)

Mean	Before	After	p
Blood leucocyte (mean; / ul)	**21053**	**17000**	**0.008**
Blood Basofil count (median; %)	0	0	0.48
Blood Eosinofil count (mean; %)	1.8	2.67	0.274
Blood neutrofil count (mean; %)	82.27	79.93	0.37
Blood Limfosit count (median; %)	8	8	0.75
Blood Monosit count (mean; %)	6.93	7.4	0.4
PCT (median; ng/ml)	0.83	0.67	0.67
Body temperature (median; °C)	**37.9**	**37.3**	**0.003**

Efficacy of **Colistin plus Tigecycline** to several inflammatory parameters (n=11)

Mean	Before	After	p
Blood leucocyte (mean; / ul)	21772,73	17936,36	0.149
Blood Basofil count (median; %)	0.36	0.36	1
Blood Eosinofil count (mean; %)	2	1,45	0,389
Blood neutrofil count (mean; %)	82.82	84.91	0.356
Blood Limfosit count (median; %)	7.64	7.09	1
Blood Monosit count (mean; %)	**7.18**	**6.18**	**0.041**
PCT (median; ng/ml)	1.012	3.31	0.104
Body temperature (median; °C)	**37.58**	**37.12**	**0.000**

Efficacy of Colistin plus Carbapenem /Tigecycline

- **Both combination therapies showed efficacy in lowering body temperature after drug administration ($p<0.05$)**

- **Blood leukocyte count also significantly decreased in patients' with Colistin-Carbapenem regimen ($p<0.05$)**
  - **Carbapenem used is Meropenem**

Discussion

- Low sample size due to incomplete data, limited number of patient with Colistin usage
- About Colistin in Indonesia
  - Colistin: Intravenous route are not widely available in Indonesia, only oral is available
  - Colistin used in this study : Colisthimethate sodium

- MIC of Meropenem to *A. baumannii* in this study were 8-32 mg/L
  Still consider to use in combination with other agent
- Inhibition zone of Colistin against *A. baumannii* were all showed sensitive (≥ 14 mm)

Discussion (2)

- The addition of Colistin based combination with meropenem indicate a synergistic effect
- This result consistent with research of Bing fan et al

- Colistin plus meropenem administration displayed synergistic effects after both 24 h and 48 h of treatment

- Colistin as monotherapy still debatable
  - Colistin monotherapy was as good as in combination (metaanalyses of Zhijin)
  - Colistin monotherapy, six studies involving 491 patients were analyzed and the results were in concordance with the findings of the colistin-based combination therapy group. [Zhijin, et all]

Bing Fan et al . Activity of Colistin in Combination with Meropenem, Tigecycline, Fosfomycin, Fusidic Acid, Rifampin or Sulbactam against Extensively Drug-Resistant *Acinetobacter baumannii* in a Murine Thigh-Infection Model. PLoS One 2016; 11(6): e0157757.

Zhijin, et all. Meta-analysis of colistin for the treatment of *Acinetobacter baumannii* infection. Sci Rep. 2015; 5: 17091.

Conclusion

Colistin-Carbapenem and Colistin-Tigecyline combination therapy can be an option for treating patients with pneumonia caused by multidrug-resistant Acinetobacter baumannii

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Баярлалаа
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감사합니다
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