2022 호흡기 감염병연구회 심포지엄

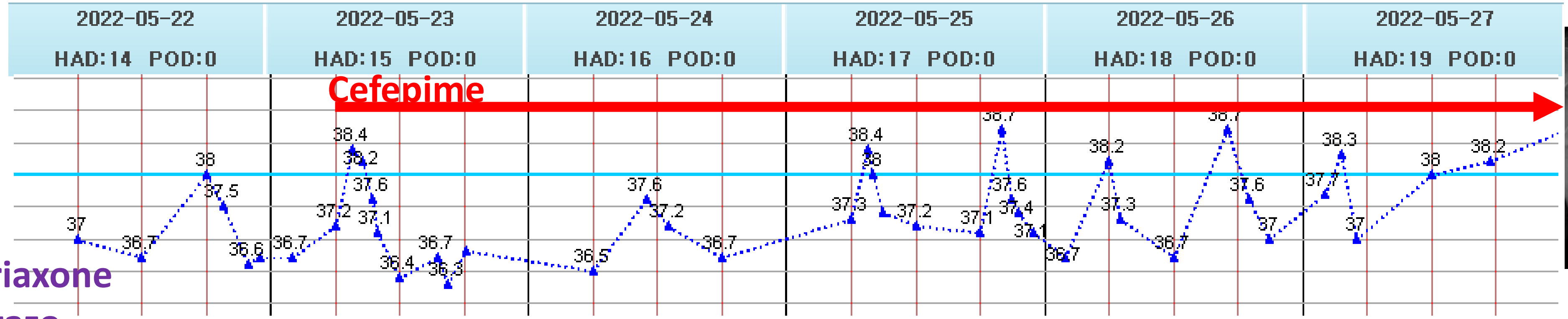
성인 병원획득폐렴 진료의 최신 지견 및 지침 개발

경험적 항생제 용법
(Initial Empirical Antibiotics in the HAP/VAP)

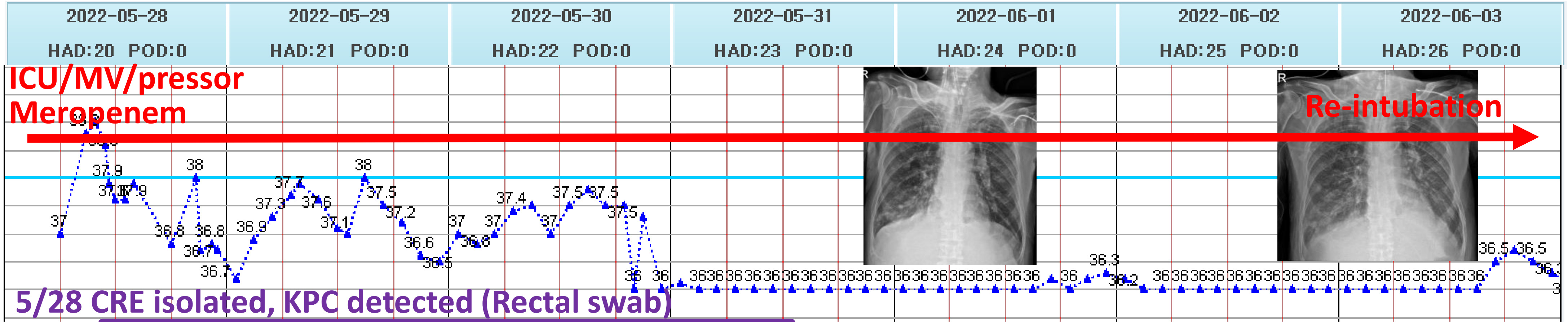
순천향대학교 부천병원
호흡기알레르기내과 백애린

- No conflicts of interest to declare.

M/81
NSCLC on CTx.
3/20-3/25 입원
4/2 - 4/6 입원
5/9- 입원
5/10-5/15 Ceftriaxone
5/16-5/22 Pip/tazo



2022-05-26	장안수	입원	완료	2022-05-30 08:2	2022-05-31 14:5	Culture & Sensitivity(Respiratory)	Sputum	Throat normal Flora	-
2022-05-26		입원	완료	2022-05-30 08:2	2022-05-31 15:2	Gram's Stain	Sputum	6 Grade(EP <10, WBC <10), Rare, Rare	-
2022-05-26		입원	완료	2022-05-30 08:2	2022-05-31 15:2	Gram stain, Culture & Sensitivity(R	Sputum		-
2022-05-28		입원	완료	2022-05-30 08:1	2022-05-31 14:5	Culture & Sensitivity(Respiratory)	Sputum	Throat normal Flora	-
2022-05-28		입원	완료	2022-05-30 08:1	2022-05-31 15:1	Gram's Stain	Sputum	1 Grade(EP >25, WBC <10), Rare, Rare	-
2022-05-28		입원	완료	2022-05-30 08:1	2022-05-31 15:1	Gram stain, Culture & Sensitivity(R	Sputum		-
2022-05-28		입원	완료	2022-05-28 21:3	2022-06-02 21:4	Blood culture (2nd)	Blood	No growth 5 day	-
2022-05-28		입원	완료	2022-05-28 21:3	2022-06-02 21:3	Blood culture (1st)	Blood	No growth 5 day	-
2022-05-26		입원	중간	2022-05-27 09:1	2022-06-24 11:3	AFB Culture	Sputum	No growth after 4weeks	-
2022-05-26		입원	완료	2022-05-27 09:1	2022-05-27 14:5	AFB smear [concentration]	Sputum	No acid fast bacilli	-
2022-05-26		입원	중간	2022-05-27 09:1	2022-06-24 11:3	AFB smear & culture	Sputum		-
2022-05-26		입원	완료	2022-05-27 08:0	2022-05-29 08:1	Culture & Sensitivity(Genitourinary)	Urine, clean vo	Growth	Candida albicans
2022-05-26		입원	완료	2022-05-27 08:0	2022-05-28 12:2	Gram's Stain	Urine, clean vo	Few, Few	-
2022-05-26		입원	완료	2022-05-27 08:0	2022-05-29 08:1	Gram stain, Culture & Sensitivity(G	Urine, clean vo		-
2022-05-26		입원	완료	2022-05-26 20:4	2022-05-31 21:1	Blood culture (2nd)	Blood	No growth 5 day	-
2022-05-26		입원	완료	2022-05-26 20:4	2022-05-31 21:1	Blood culture (1st)	Blood	No growth 5 day	-
2022-05-25		입원	완료	2022-05-25 13:5	2022-05-25 15:2	C.diffcile Test(CDT) [MEI]	Stool	Negative, Negative	-
2022-05-23		입원	완료	2022-05-23 13:5	2022-05-28 14:0	Blood culture (1st)	Blood	No growth 5 day	-
2022-05-2		**입원**	**완료**	**2022-05-23 1**	**2022-05-28 1**	**Blood culture (2nd)**	**Blood**	**No growth 5 day**	-



Gram stain, Culture & Sensitivity(Others

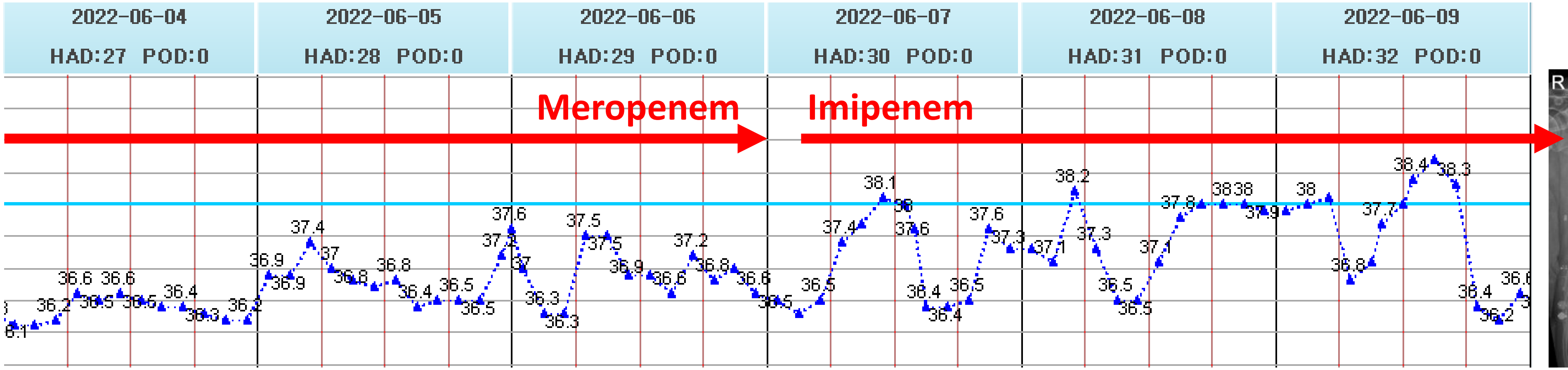
MRAB screening test (Multidrug Resista

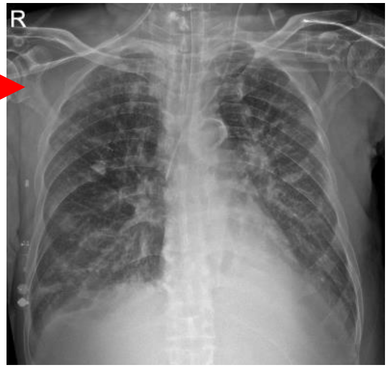
CRE Follow Up Test

Carbapenemase gene PCR(surveillanc

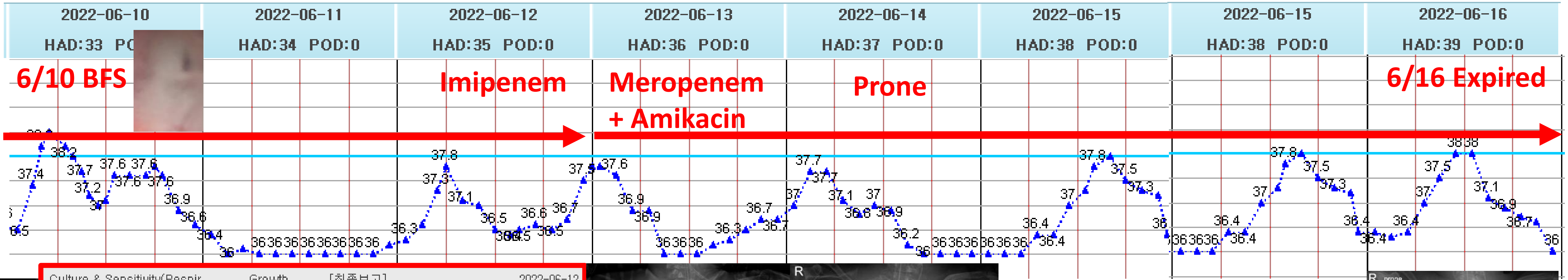
[진단검사] 미생물유전[Rectal swab] -검체번호:I233K0RQ0	채취일시 2022/05/28 21:31
Carbapenemase gene PCR(surveillance) [Real-t	양성(KPC detected)

2022-06-03		입원	완료	2022-06-03 14:(	2022-06-05 10:(	Culture & Sensitivity(Genitourinary)	Urine, clean vc	Growth	Enterococcus faecalis, Candida albicans
2022-06-03		입원	완료	2022-06-03 14:(	2022-06-04 13::	Gram's Stain	Urine, clean vc	Few, Rare, Some	-
2022-06-03		입원	완료	2022-06-03 14:(	2022-06-05 10:(	Gram stain, Culture & Sensitivity(G	Urine, clean vc		-
2022-06-03		입원	완료	2022-06-03 10:!	2022-06-09 09::	(1-3)-β-D-Glucan	Serum	Positive : 114.6	-
2022-06-02		입원	중간	2022-06-03 10:(	2022-06-24 12:'	AFB Culture	Sputum	No growth after 3weeks	-
2022-06-02		입원	완료	2022-06-03 10:(	2022-06-03 16:'	AFB smear [concentration]	Sputum	No acid fast bacilli	-
2022-06-02		입원	중간	2022-06-03 10:(	2022-06-24 12:'	AFB smear & culture	Sputum		-
2022-06-0		**입원**	**완료**	**2022-06-03 0**	**2022-06-04 1**	**Culture & Sensitivity(Respirat**	**Sputum**	**Throat normal Flora**	-
2022-06-03		입원	완료	2022-06-03 08:'	2022-06-04 13:'	Gram's Stain	Sputum	6 Grade(EP <10, WBC <10), No organism(ba(	-
2022-05-31		입원	완료	2022-05-31 08:'	2022-06-02 15:(	Culture & Sensitivity(Respiratory)	Sputum	Throat normal Flora	-
2022-05-31		입원	완료	2022-05-31 08:'	2022-06-02 15:(	Gram's Stain	Sputum	5 Grade(EP <10, WBC >25), No organism(ba(	-
2022-05-31		입원	완료	2022-05-31 08:'	2022-06-02 15:(	Gram stain, Culture & Sensitivity(R	Sputum		-
2022-05-28		입원	완료	2022-05-30 13:'	2022-05-31 12::	Culture & Sensitivity(Others)	Nasal Swab	No MRSA isolated	-
2022-05-28		입원	완료	2022-05-30 13:'	2022-05-31 12::	Gram stain, Culture & Sensitivity(O	Nasal Swab		-
2022-05-28		입원	완료	2022-05-30 13:(	2022-05-31 12:(	MRAB screening test (Multidrug R	Rectal swab	No MRAB isolated	-
2022-05-2		**입원**	**완료**	**2022-05-30 1**	**2022-06-02 0**	**CRE Follow Up Test**	**Rectal swab**	**CRE isolated(신환)**	-

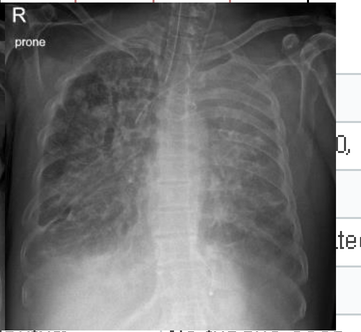




2022-06-05	백애린	입원	완료	2022-06-06 09:(	2022-06-07 10::	Culture & Sensitivity(Respiratory)	Sputum	Throat normal Flora	-
2022-06-05	백애린	입원	완료	2022-06-06 09:(	2022-06-07 10:4	Gram's Stain	Sputum	5 Grade(EP <10, WBC >25), Rare	-
2022-06-05	백애린	입원	완료	2022-06-06 09:(	2022-06-07 10:4	Gram stain, Culture & Sensitivity(R	Sputum		-
2022-06-06	백애린	입원	완료	2022-06-06 08:5	2022-06-07 10::	Culture & Sensitivity(Respiratory)	Sputum	Throat normal Flora	-
2022-06-06	백애린	입원	완료	2022-06-06 08:5	2022-06-07 10:3	Gram's Stain	Sputum	5 Grade(EP <10, WBC >25), No organism(bac	-
2022-06-06	백애린	입원	완료	2022-06-06 08:5	2022-06-07 10:3	Gram stain, Culture & Sensitivity(R	Sputum		-
2022-06-06	백애린	입원	완료	2022-06-06 08:4	2022-06-07 10:1	MRAB screening test (Multidrug R	Rectal swab	MRAB isolated	-
2022-06-05	백애린	입원	완료	2022-06-06 08:4	2022-06-07 10::	CRE Follow Up Test	Rectal swab	CRE isolated	-
2022-06-05	백애린	입원	완료	2022-06-06 08:4	2022-06-07 10:1	Culture & Sensitivity(Others)	Nasal Swab	No MRSA isolated	-
2022-06-05	백애린	입원	완료	2022-06-06 08:4	2022-06-07 10:1	Gram stain, Culture & Sensitivity(O	Nasal Swab		-
2022-06-06	백애린	입원	완료	2022-06-06 08:1	2022-06-06 17:5	Fungus Direct Microscopy [진균검	Sputum	No fungus seen	-
2022-06-06	백애린	입원	중간	2022-06-06 08:1	____-__-__ __:_	Fungus stain & Culture [Respirato	Sputum		-
2022-06-04	백애린	입원	완료	2022-06-04 09:(	2022-06-06 08:5	Culture & Sensitivity(Respiratory)	Sputum	Throat normal Flora	-
2022-06-04	백애린	입원	완료	2022-06-04 09:(	2022-06-06 09:(	Gram's Stain	Sputum	3 Grade(EP >25, WBC >25), Rare, Rare, Rare	-
2022-06-04	백애린	입원	완료	2022-06-04 09:(	2022-06-06 09:(	Gram stain, Culture & Sensitivity(R	Sputum		-



Culture & Sensitivity(Respir	Growth	[최종보고]	2022-06-12
→ Klebsiella pneumoniae	완료(Moderate)		2022-06-1
ESBL	Neg	NEG	2022-06-12 08:17
Ampicillin	>=32	R	2022-06-12 08:17
Aztreonam	>=64	R	2022-06-12 08:17
Cefepime	>=64	R	2022-06-12 08:17
Cefotaxime	>=64	R	2022-06-12 08:17
Ceftazidime	>=64	R	2022-06-12 08:17
Gentamicin	>=16	R	2022-06-12 08:17
Cefazolin	>=64	R	2022-06-12 08:17
Ertapenem	>=8	R	2022-06-12 08:17
Piperacillin/tazobactam	>=128	R	2022-06-12 08:1
Tigecycline	>=8	R	2022-06-12 08:17
Amoxicillin/clavulanic acid	>=32	R	2022-06-12 08:1
Amikacin	<=2	S	2022-06-12 08:17
Cefoxitin	>=64	R	2022-06-12 08:17
Ciprofloxacin	>=4	R	2022-06-12 08:17
Imipenem	>=16	R	2022-06-12 08:17
Trimethoprim/sulfamethoxazole	>=320	R	2022-06-12 0



			Acinetobacter bauma
		0, WBC <10), Rare	-
			-
		ted	-
			-
Direct Microscopy [진균검	Sputum	No fungus seen	-
stain & Culture [Respirato	Sputum		-
& Sensitivity(Respirat	Sputum	Growth	Acinetobacter baumannii
& Sensitivity(Respiratory)	Sputum	Growth	Klebsiella pneumoniae
Stain	Sputum	6 Grade(EP <10, WBC <10), Rare	-
ain, Culture & Sensitivity(R	Sputum		-
& Sensitivity(Respirat	Bronchial Wa	Growth 6/10 BFS	Klebsiella pneumoniae
Stain	Bronchial Wasl	No WBC, Rare, Rare	-
ain, Culture & Sensitivity(R	Bronchial Wasl		-
ulture (1st)	Blood	No growth 5 day	-
ulture (3rd)	Blood	No growth 5 day	-
ulture (2nd)	Blood	No growth 5 day	-

2022-06-1	입원	완료	2022-06-10 0	2022-06-12 0	Culture & Sensitivity(Respirat	Sputum	Growth	Klebsiella pneumoniae

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Why is the initial empirical antimicrobial therapy important in HAP/VAP? (Benefits vs. Harms)

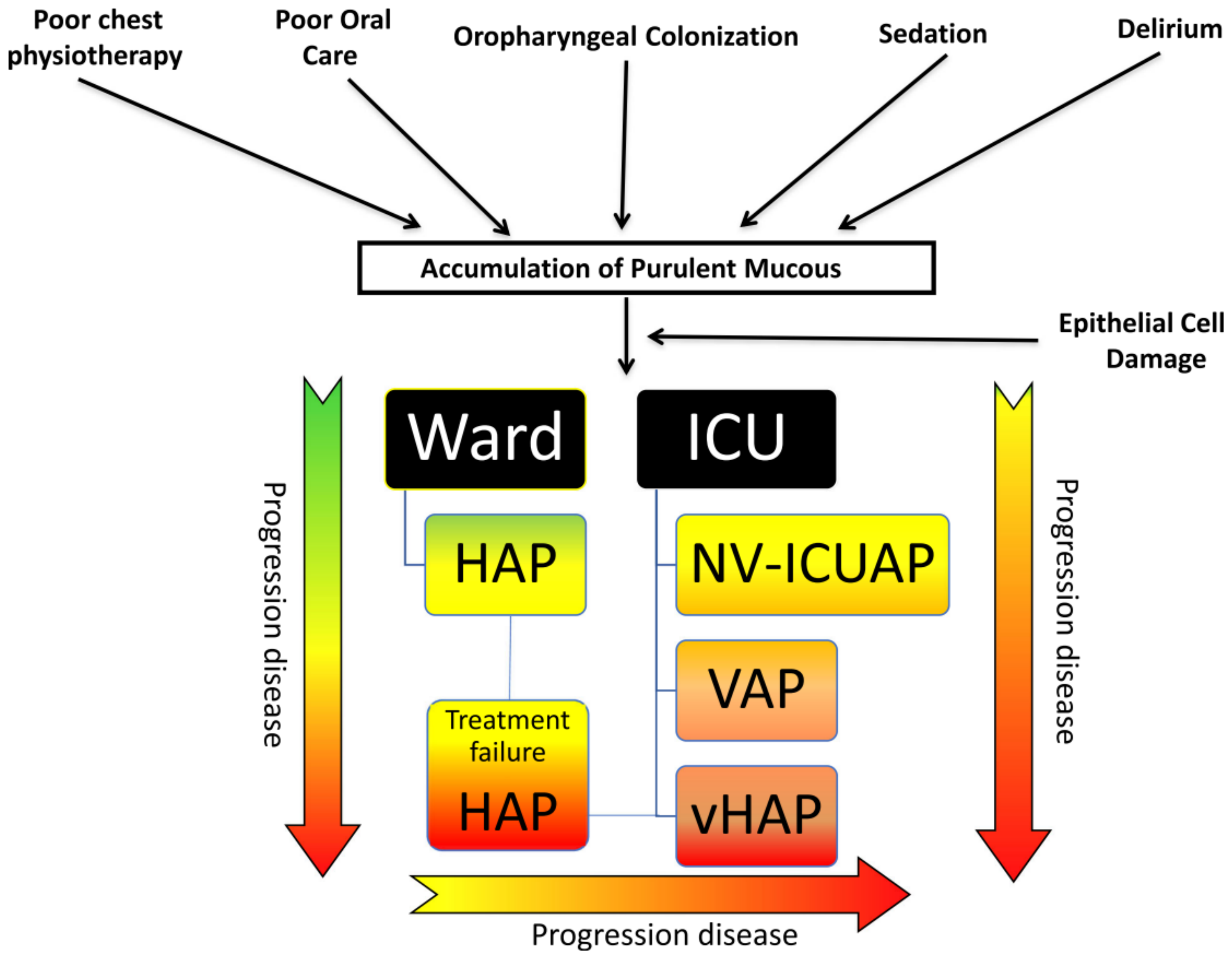
Sicker patients in the hospital or ICU

Increasing Multi-Drug Resistant Organisms (MDROs)

- Inappropriate Empiric Therapy(IET)
- Mortality
- Length of stay (LOS)
- Costs

- Development of future antibiotic resistance (Individual & Environmental)
- Drug adverse effects
- Costs

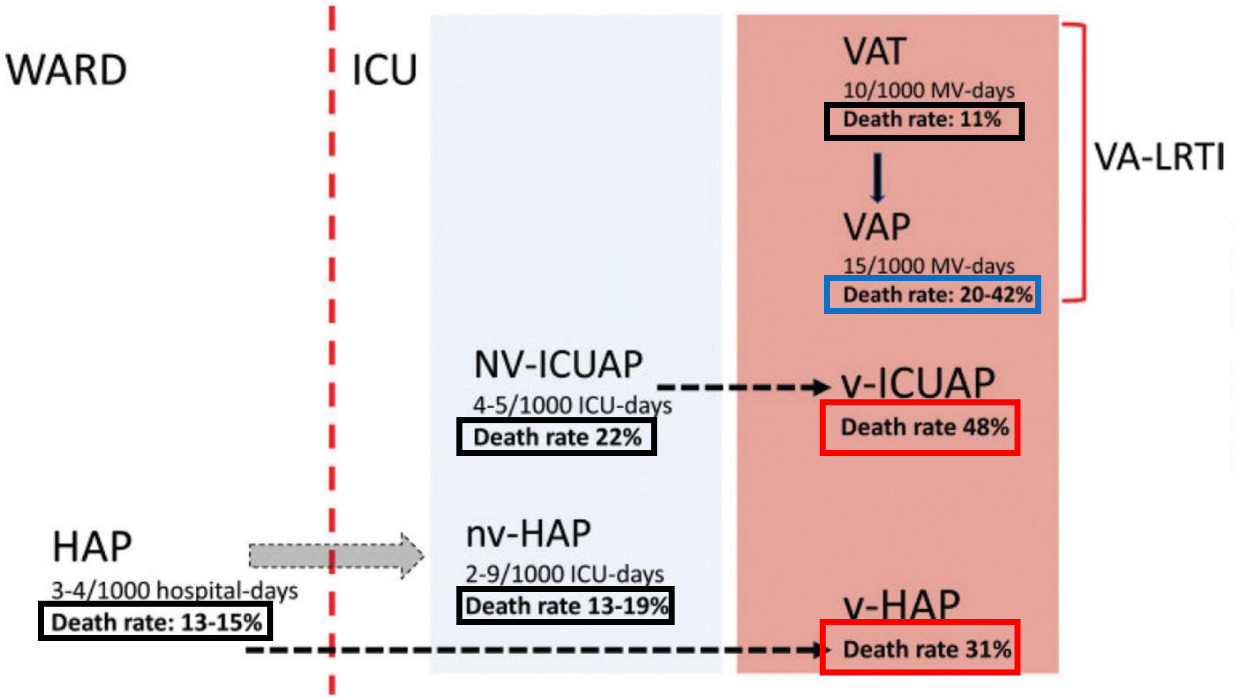
Pathogenesis of Nosocomial Pneumonia (HAP/VAP)



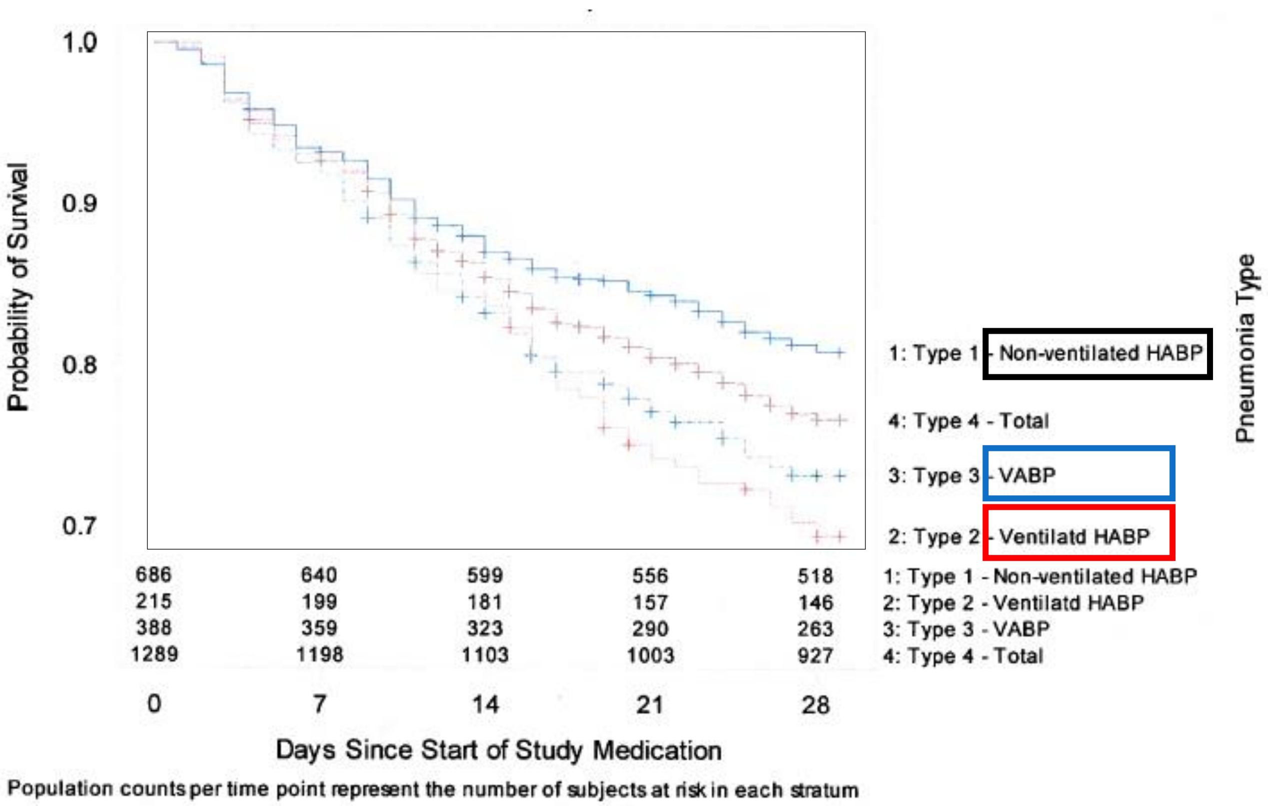
Zaragoza, R., et al. (2020)

Spectrum of Nosocomial pneumonia

–different prognosis?



Wicky, P. H., et al. (2022)



Talbot, G. H., et al. (2019)

Spectrum of Nosocomial pneumonia

–different prognosis?

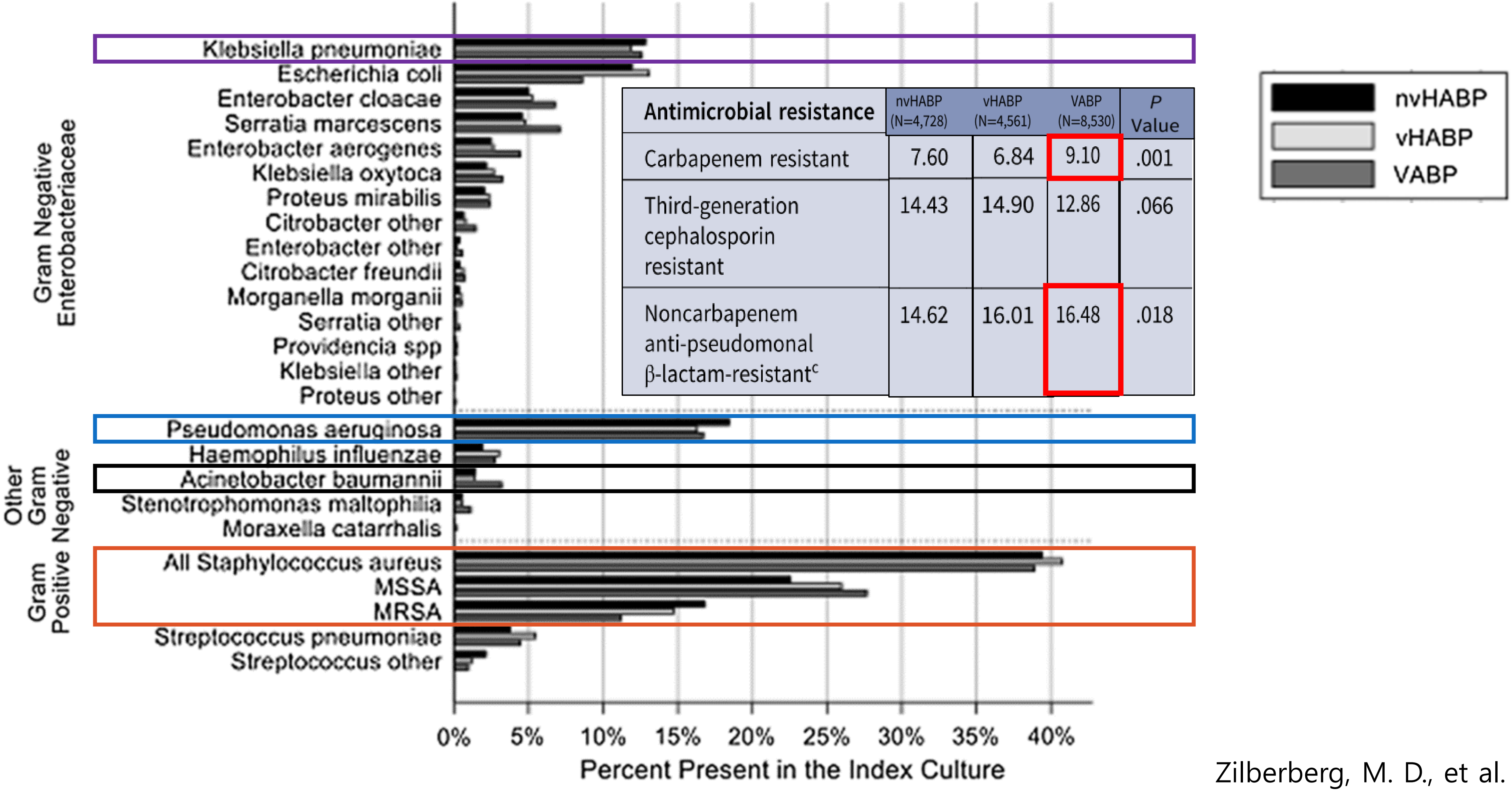
A Multicenter Retrospective Cohort Study, United States, 2014–2019

Outcome	Nonventilated Hospital-Acquired Bacterial Pneumonia n = 4,728	%	Ventilated Hospital-Acquired Bacterial Pneumonia n = 4,561	%	Ventilator-Associated Bacterial Pneumonia n = 8,530	%	p
Hospital mortality	553	11.70	1,330	29.16	1,813	21.25	< 0.001
30-d readmission	1,021	24.46	728	22.52	1,266	18.83	< 0.001
Discharge destination							
Home	863	18.25	391	8.57	785	9.20	< 0.001
Home with healthcare	842	17.81	387	8.48	583	6.83	
SNF	1,927	40.76	1,930	42.32	4,395	51.52	
Died	332	7.02	293	6.42	436	5.11	
Hospice	553	11.70	1,330	29.16	1,813	21.25	
Other	211	4.46	230	5.04	518	6.07	
Hospital LOS all, d							
Mean (SD)	23.4 (24.6)		25.6 (20.7)		27.8 (24.1)		< 0.001
Median (IQR)	17 (11–27)		21 (14–31)		22 (15–32)		< 0.001
Hospital costs all, $							
Mean (SD)	59,002 (67,448)		82,372 (80,624)		101,386 (106,229)		< 0.001
Median (IQR)	39,911 (24,142–69,129)		62,464 [39,149–99,323]		77,657 [50,823–122,419]		< 0.001

Zilberberg, M. D., et al. (2022)

Etiology of HAP/VAP

Microbiology, empiric therapy and its impact on the outcomes of nonventilated hospital-acquired, ventilated hospital-acquired, and ventilator-associated bacterial pneumonia in the United States, 2014–2019 (Multicenter retrospective cohort study within Premier Research database)



Antimicrobial resistance	nvHABP (N=4,728)	vHABP (N=4,561)	VABP (N=8,530)	*P* Value
Carbapenem resistant	7.60	6.84	9.10	.001
Third-generation cephalosporin resistant	14.43	14.90	12.86	.066
Noncarbapenem anti-pseudomonal β-lactam-resistant[c]	14.62	16.01	16.48	.018

Zilberberg, M. D., et al. (2022)

Etiology of HAP/VAP

Table 1 Microbiology and main resistance profile of microorganism causing VAP, VAT and HAP in non-ventilated patients treated in ICU (data from studies published from 2010 to 2019)

Reference	Type of infection	Microbiology				
Ferrer et al. (2010)	HAP	*S. aureus*, 17.7%	*P. aeruginosa*, 17.7%	*E.coli*, 6.5%	*Enterobacter* spp., 4.3%	*K. pneumoniae*, 3.2%
Esperatti et al. (2016)	VAP	*P. aeruginosa*, 24%	*S. aureus*, 23%	*E. coli*, 7%	*Enterobacter* spp., 6%	*H. influenzae*, 4%
Restrepo et al. (2013)	VAP	*S. aureus*, 38.7%	*H. influenzae*, 23.4%	*P. aeruginosa*, 14.7%	*k. pneumoniae*, 11.5%	*E. coli*, 11.1%
		MDR, 30%				
Quartin et al. (2013)	VAP	*S. aureus*, 60.3%	*P. aeruginosa*, 9.4%	*Acinetobacter* spp., 7.3%	*Klebsiella* spp., 6.8%	*Enterobacter* spp., 5.1%
Nseir et al. (2014)	VAT	*P. aeruginosa*, 34.4%	*S. aureus*, 20.5%	*A. baumanii*, 11.5%	*K. oxytoca*, 10.6%	*Enterobacter* spp., 9.8%
		MDR, 36.8%				
Martín-Loeches et al (2015)	VAT	*P. aeruginosa*, 25%	*S. aureus*, 23%	*Klebsiella* spp., 15%	*E. coli*, 12%	*Enterobacter* spp., 11%
		MDR, 61%				
	VAP	*P. aeruginosa*, 24%	*S. aureus*, 24%	*Klebsiella* spp., 14%	*Enterobacter* spp., 12%	*E. coli*, 11%
		MDR, 61%				
ECDC (2018)	VAP	*P. aeruginosa*, 20.8%	*S. aureus*, 17.8%	*Klebsiella* spp., 16.1%	*E. coli*, 13.3%	*Enterobacter* spp., 10.3%
Koulenti et al. (2017)	HAP	*Enterobacteriaceae*, 32.9%	*S. aureus*, 24.9%	*P. aeruginosa*, 17.4%	*A. baumanii*, 15.4%	
ENVIN-HELICS (2018)	VAP	*P. aeruginosa*, 23.8%	*S. aureus*, 13.5%	*Klebsiella* spp., 10.3%	*E. coli*, 9.1%	*Enterobacter* spp., 8.6%
		PIP/TAZ R, 34.1% Carba R, 37.9% Colistin R, 8.6%	MRSA, 12.7%	PIP/TAZ R, 50% Carba R, 23.5% 3°G cef R, 37%	PIP/TAZ R, 21.7% Carba R, 0% 3°G cef R, 12.5%	
Pulido et al. (2018)	VAP	*P. aeruginosa*, 21.1%	*A. baumanii*, 17.9%	*K. pneumoniae*, 15.6%	*S. aureus*, 13.3%	*E. coli*, 7.8%
Huang et al (2018)	VAP	*A. baumanii*, 33.9%	*K. pneumoniae*, 23.6%	*P. aeruginosa*, 19.8%	*S. aureus*, 7.1%	*S. maltophilia*, 3.8%
		Carba R, 76.4%	Carba R, 44%	Carba R, 59.5%	MRSA, 60%	
Cantón-Bulnes et al. (2019)	VAT	*P. aeruginosa*, 24.5%	*H. influenzae*, 18.9%	*E. coli*, 9.4%	*S. aureus*, 9.4%	*K. pneumoniae*, 7.5%
Ibn Saied et al. (2013)	VAP	*P. aeruginosa*, 33.5%	*Enterobacteriaceae*, 32.3%	*S. aureus*, 19%	*S. pneumoniae*, 4.9%	*S. maltophilia*, 4.7%

carba carbapenem, *HAP* hospital-acquired pneumonia, *MDR* multidrug resistant, *VAP* ventilator-associated pneumonia, *VAT* ventilator-associated tracheobronchitis, *PIP/TAZ* piperacillin/tazobactam, *R* resistance, *3°G cef* 3° generation cephalosporin

*Trial designed to compare MRSA pneumonia treatment, special effort to include patients with MRSA pneumonia

Zaragoza, R., et al. (2020)

Etiology of HAP/VAP

Clinical and microbiological characteristics of adults with hospital-acquired pneumonia : a 10-year prospective observational study in China

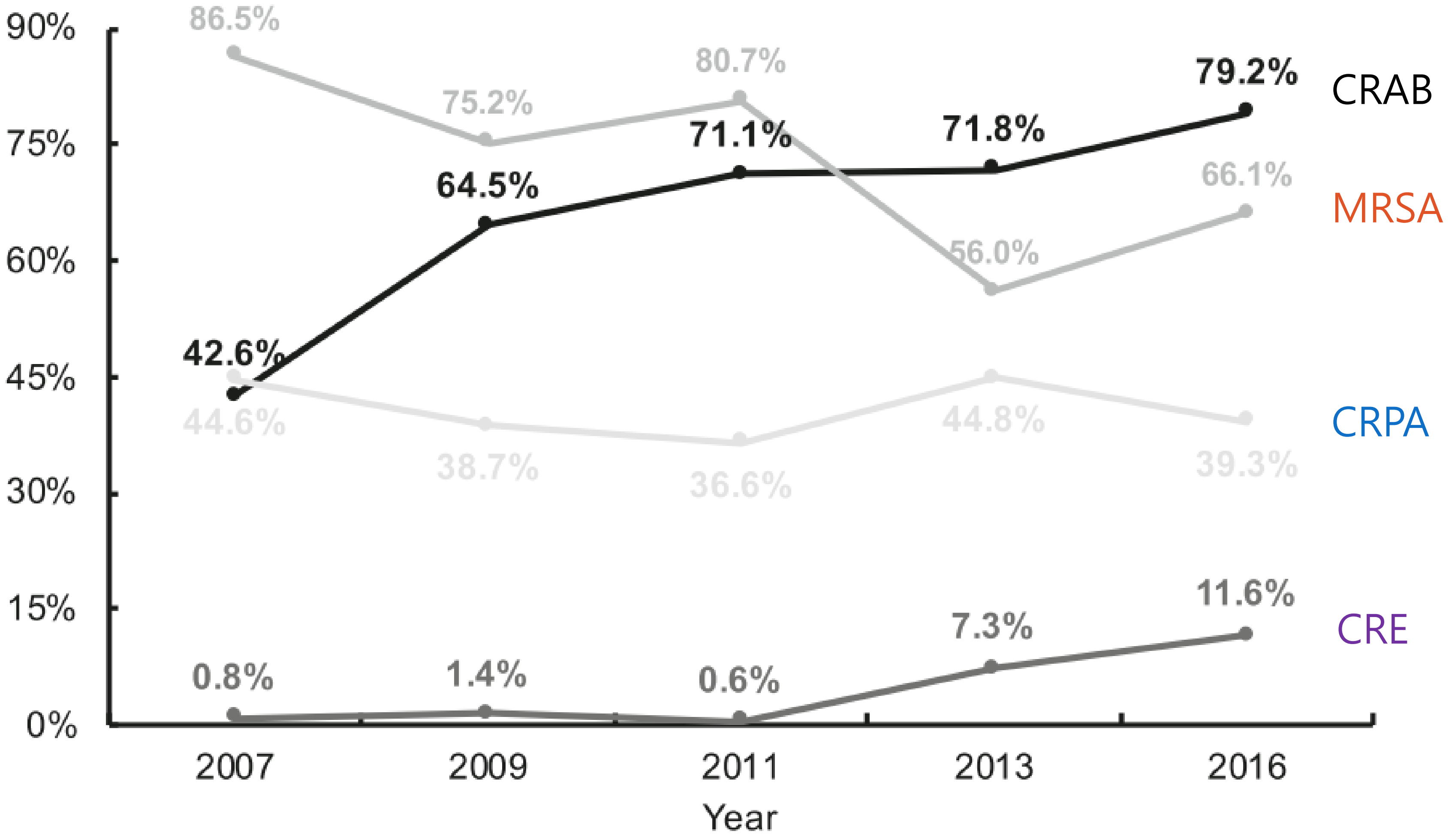
(Chinese Antimicrobial Resistance Surveillance of Nosocomial Infections network, 2007–2016)

Speciesa	VAP $n = 1181$(%)		Non-VAP $n = 1749$ (%)	Total $n = 2930$ (%)	p value
Acinetobacter baumannii	374 (31.7)	>	375 (21.4)	749 (25.6)	<0.001*
Pseudomonas aeruginosa	250 (21.2)		338 (19.3)	588 (20.1)	0.240
Klebsiella pneumoniae	142 (12.0)	<	310 (17.7)	452 (15.4)	<0.001*
Staphylococcus aureus	156 (13.2)		212 (12.1)	368 (12.6)	0.415
Escherichia coli	60 (5.1)		160 (9.1)	220 (7.5)	<0.001*
Pseudomonas maltophilia	57 (4.8)		77 (4.4)	134 (4.6)	0.654
Enterobacter cloaca	38 (3.2)		81 (4.6)	119 (4.1)	0.071
Serratia marcescens	11 (0.9)		25 (1.4)	36 (1.2)	0.303
Burkholderia cepacia	25 (2.1)		10 (0.6)	35 (1.2)	<0.001*
Enterobacter aerogenes	7 (0.6)		22 (1.3)	29 (1.0)	0.112
Streptococcus pneumoniae	2 (0.2)		22 (1.3)	24 (0.8)	0.003
Citrobacter freundii	8 (0.7)		13 (0.7)	21 (0.7)	0.987
Proteus mirabilis	7 (0.6)		14 (0.8)	21 (0.7)	0.667
Klebsiella oxytoca	7 (0.6)		12 (0.7)	19 (0.6)	0.941
Staphylococcus haemolyticus	2 (0.2)		9 (0.5)	11 (0.4)	0.234
Staphylococcus epidermidis	1 (0.1)		9 (0.5)	10 (0.3)	0.102

Yin, Y., et al. (2021)

Etiology of HAP/VAP (Prevalence of MDRO)

Prevalence of CRAB, CRPA, CRE, and MRSA in HAP patients
: a 10-year prospective observational study in China
(Chinese Antimicrobial Resistance Surveillance of Nosocomial Infections network, 2007–2016)



Yin, Y., et al. (2021)

의료관련감염관리 : 제26권 제2호 2021
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2019.7 ~ 2020 6
256 hospitals (340 units), Korea

전국의료관련감염감시체계 중환자실 부문 결과 보고: 2019년 7월부터 2020년 6월

Korean National Healthcare-associated Infections Surveillance System, Intensive Care Unit Module Report: Summary of Data from July 2019 through June 2020

(KONIS)

원인미생물과 주요 미생물의 항생제 내성률

주요 폐렴 원인균

-그람음성막대균(**80.2%**), 그람양성알균(18.3%)
전년도 77.7%

-흔한 원인균 순위

	전년도
• ***A. baumannii*** (**31.6%**)	41.9%
• ***K. pneumoniae*** (**17.1%**)	18.5%
• ***S. aureus*** (16.6%)	23.8%
• *P. aeruginosa* (12.4%)	16.5%

Kim, et al. (2021)

전국 중환자실 의료관련감염 감시체계(KONIS) 운영 결과

Table 3. Antimicrobial resistance rates(%) of major pathogens isolated from patients with healthcare-associated infections

Organism	Antimicrobial resistance rates		
	2006-2011	2012-2016	2017-2020
Methicillin-resistant *Staphylococcus aureus*	90.4	86.7	79.7 / 79.4 / 74.5 / 75.4
Vancomycin-resistant *Enterococcus faecalis*	3.80	3.80	6.5 / 3.9 / 3.2 / 7.3
Vancomycin-resistant *Enterococcus faecium*	40.3	48.3	43.7 / 50.7 / 55.9 / 56.6
Cefotaxime-resistant *Escherichia coli*	39.9	46.6	56.8 / 52.6 / 58.8 / 52.6
Cefotaxime-resistant *Klebsiella pneumoniae*	61.9	59.3	68.6 / 65.6 / 64.3 / 65.2
Ciprofloxacin-resistant *Escherichia coli*	52.9	56.1	61.8 / 57.6 / 61.6 / 60.8
Ciprofloxacin-resistant *Klebsiella pneumoniae*	56.8	51.6	64.3 / 62.4 / 58.3 / 61.0
Imipenem-resistant *Pseudomonas aeruginosa*	52.9	41.0	45.2 / 50.3 / 52.7 / 50.3
Imipenem-resistant *Acinetobacter baumannii*	74.8	87.5	89.1 / 89.6 / 89.3 / 89.7
Imipenem-resistant *Klebsiella pneumoniae*			12.1 / 15.1 / 18.3 / 23.5

* Antimicrobial resistance rates : No. of resistant / Total isolates × 100

Lee, et al. KONIS (2017), KONIS (2017-2020)

전국 중환자실 의료관련감염 감시체계(KONIS) 운영 결과

Table 4. Antimicrobial resistance rates(%) of major isolated pathogens

	2006	2007-2008	2008-2009	2009-2010	2010-2011	2011-2012	2012-2013	2013-2014	2014-2015	2015-2016	**2017-2020**
MRSA	92.4	89.7	88.9	91.3	90.4	89.1	86.6	87.6	85.9	83.1	**77.3**
IRAB	43.6	65.1	68.9	82.5	84.8	86.9	83.1	88.2	89.4	90.2	**89.4**

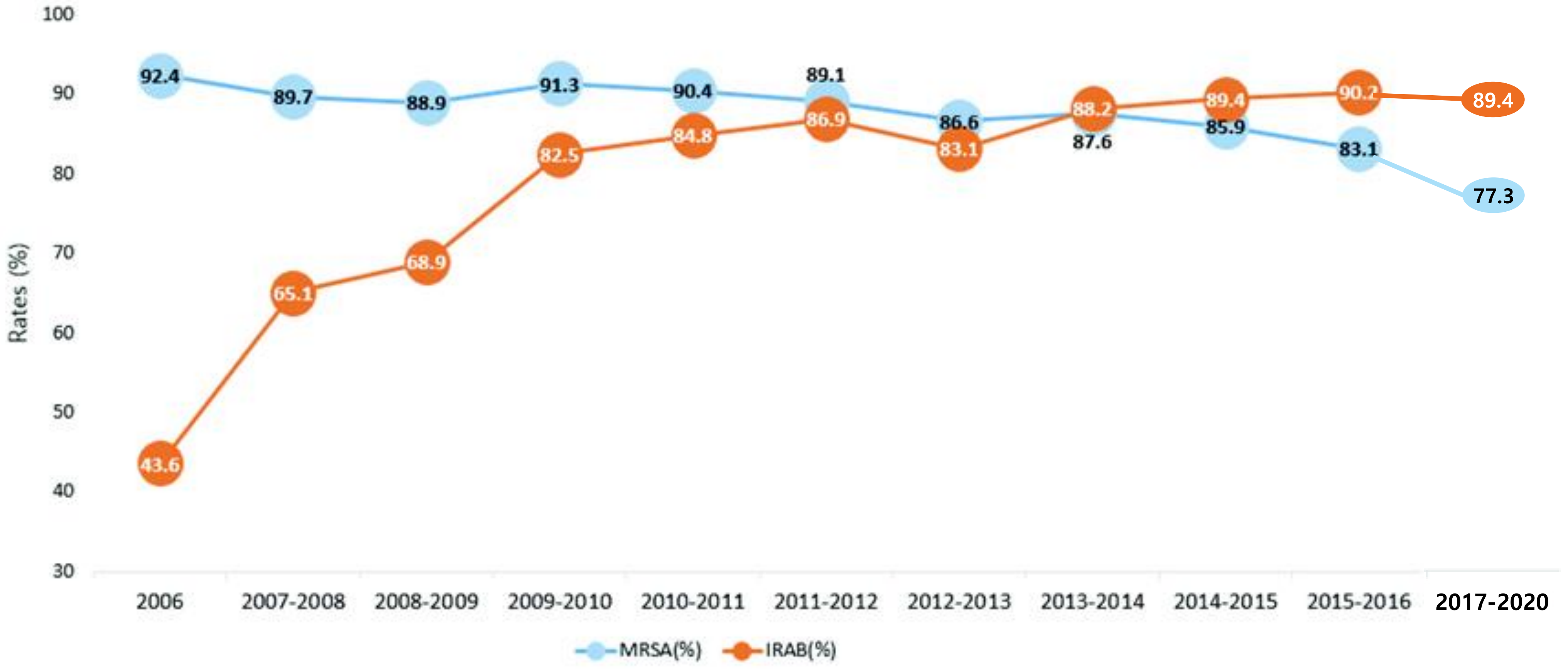


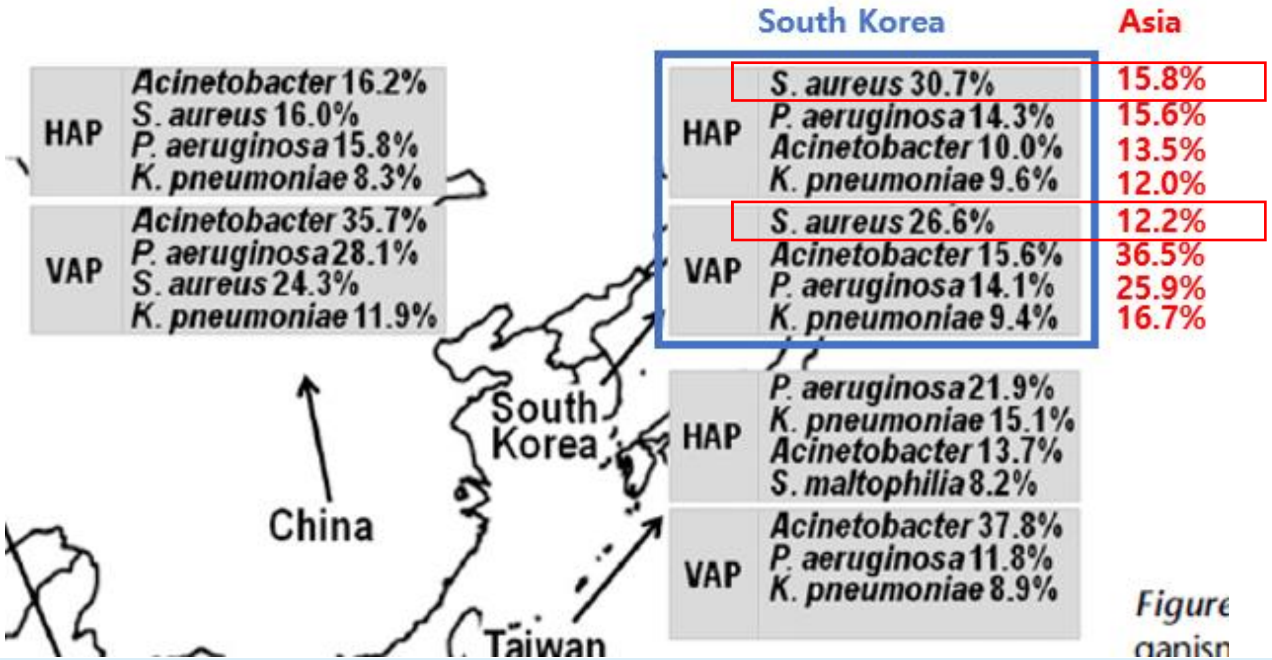
Figure 1. Antimicrobial resistance rates(%)

Modified from Lee, et al. KONIS (2017)

Etiology of HAP/VAP in Korea

High Prevalence of Multidrug-Resistant Nonfermenters in Hospital-acquired Pneumonia in Asia

2008-2009 (15 hospitals, Korea)
(Prospective multinational surveillance study in 73 hospitals, 10 Asian countries)



<MDR rates in Asia>

S. Aureus	**82.1%**
P. aeruginosa	**42.8%**
A. baumannii	**82.0%**
K. pneumoniae	**44.7%**

Risk factors for mortality

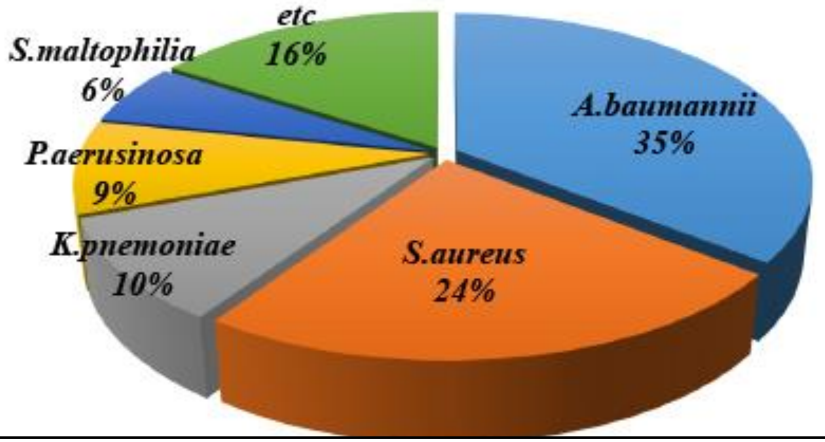
- VAP vs. HAP : OR 1.433 (0.990-2.076), p=0.057
- **ICU** vs. **Non-ICU** : **OR 0.406** (0.284-0.581), p<0.001
- **S. aureus** : **OR 0.640** (0.413-0.992), p=0.046
- A. baumannii : OR 1.303 (0.925-1.835), p=0.130
- **Discordant initial empirical antibiotic therapy** : **OR 1.542** (1.127-2.110), p=0.007

Chung, D. R., et al. (2011)

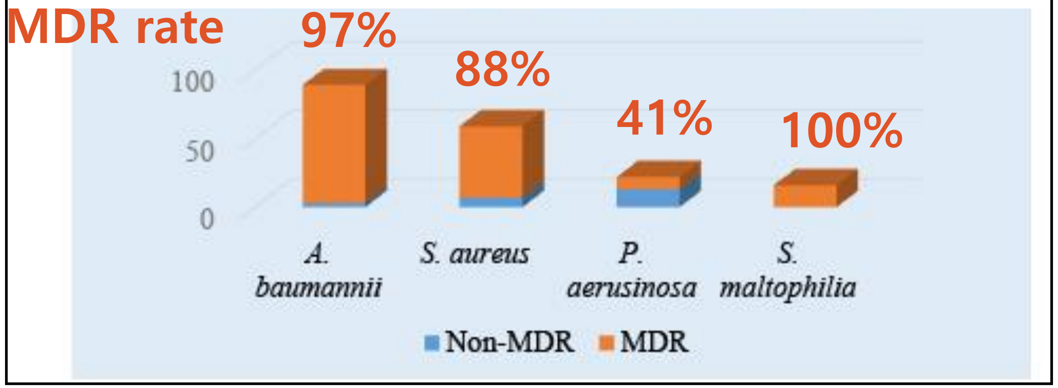
2012-2015 (5 hospitals, Korea)

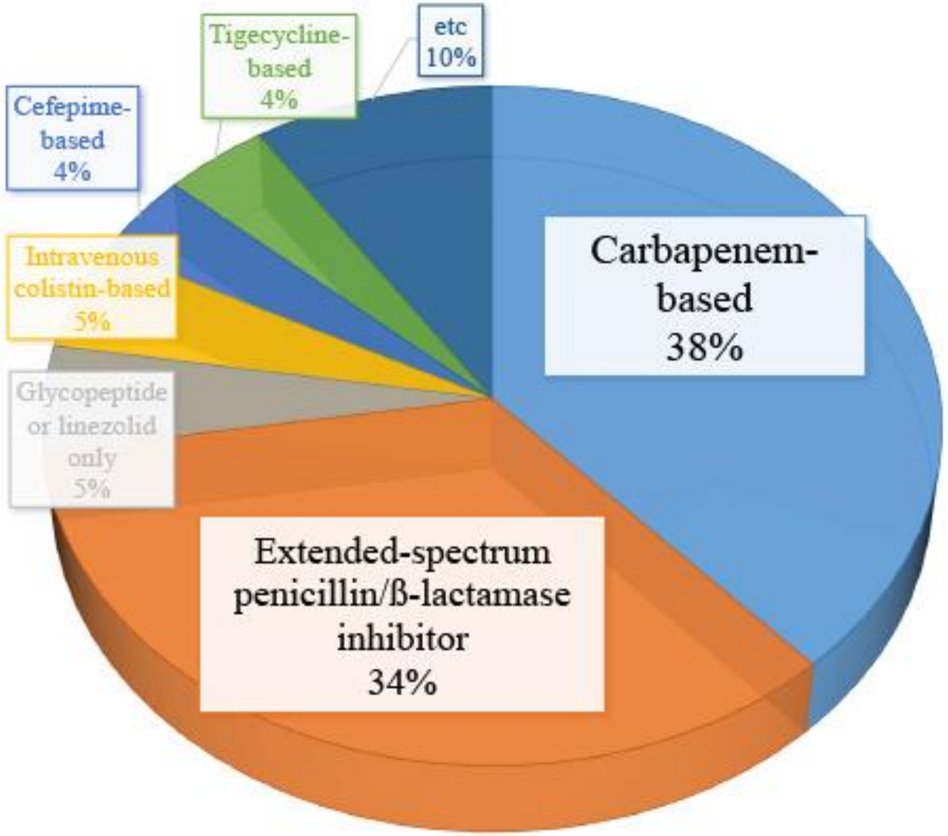
The Distribution of Multidrug-resistant Microorganisms and Treatment Status of Hospital-acquired Pneumonia/Ventilator-associated Pneumonia in Adult Intensive Care Units : A Prospective Cohort Observational Study

Discrepancy between major HAP/VAP pathogens and empirical antibiotics



*Of the 250 identified pathogens,
171 (68.4%) pathogens were multi-drug-resistant.





Empirical antibiotics during the first 48 hours

Chang, Y., et al. (2021)

Table 4. Empirical and subsequent antibiotic treatments (n = 381)

Empirical antibiotics during the first 48 hours	
Carbapenem-based	144 (38)
Extended-spectrum penicillin/β-lactamase inhibitor	131 (34)
Glycopeptide or linezolid only	20 (5)
Intravenous colistin-based	19 (5)
Cefepime-based	15 (4)
Tigecycline-based	14 (4)
Quinolone only	12 (3)
Third cephalosporin-based	9 (2)
Carbapenem + tigecycline	8 (2)
Sulbactam-based	4 (1)
Intravenous colistin + tigecycline	4 (1)
Others	1 (0.3)
Combination therapy	
Quinolone	149/369 (40)
Glycopeptide or linezolid	196/361 (54)
Inhaled colistin	20 (5)

Subsequent antibiotics from the first 48 hour forth to 2 weeks	n = 377[a]
Carbapenem-based	137 (36)
Extended-spectrum penicillin/β-lactamase inhibitor	109 (29)
Intravenous colistin-based	30 (8)
Intravenous colistin + tigecycline	20 (5)
Cefepime-based	19 (5)
Quinolone only	15 (4)
Glycopeptide or linezolid only	15 (4)
Tigecycline-based	12 (3)
Third cephalosporin-based	11 (3)
Carbapenem + tigecycline	2 (1)
Sulbactam-based	2 (1)
Others	5 (1)
Combination therapy	
Quinolone	127 (34)
Glycopeptide or linezolid	176 (47)

Appropriate empirical antibiotics as a prognostic factor for 28-day mortality

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Appropriate empirical antibiotics	0.415 (0.167–1.032)	0.059	0.282 (0.092–0.859)	0.026
Appropriate antibiotics from 48 hours to 2 weeks	0.499 (00.190–1.310)	0.158		

Chang, Y., et al. (2021)

2019 (13 hospitals, Korea)

trd Tuberculosis & Respiratory Diseases

Characteristics, Management, and Clinical Outcomes of Patients with Hospital-Acquired and Ventilator-Associated Pneumonia: A Multicenter Cohort Study in Korea

<MDR rates of most common pathogens>

1) 32.2% : Acinetobacter (MDR 98.5%)
2) **17.1% : Pseudomonas (MDR 83.3%)**
3) 34.1% : Enterobacteriaceae **(MDR 37.5%)**
   (16.6%: K. pneumoniae)
4) **11.4% : S. aureus (MRSA 79.2%)**

MDR pathogen identified[*], n (%)	138 (70.4)
Acinetobacter species	67 /68
Pseudomonas aeruginosa	30 /36
Enterobacteriaceae	27 /72
Staphylococcus aureus	19 /24
Enterococcus species	4 /5

Table 3. Bacterial pathogen identified in patients with hospital-acquired and ventilator-associated pneumonia

Variable	No. (n=211)
Gram-positive pathogens	
Staphylococcus aureus	24
Streptococcus pneumonia	7
Enterococcus faecium	5
Nonstaphylococcus aureus Staphylococcus species	4
Others[*]	5
Gram-negative pathogens	
Acinetobacter baumannii	68
Pseudomonas aeruginosa	36
Klebsiella pneumoniae	35
Escherichia coli	11
Sternotrophomonas maltophilia	11
Enterobacter cloacae	10
Serratia marcescens	5
Proteus species	4
Klebsiella aerogenes	3
Moraxella catarrhalis	2
Burkholderia cephacia	2
Citrobacter species	2
Others[†]	2

Ko, R. E., et al. (2021)

Table 4. Treatment for hospital-acquired and ventilator-associated pneumonia

Variable	Value (n=526)
Initial empirical antibiotics	
Extended-spectrum penicillin/ beta-lactamase inhibitor	312 (59.3)
Respiratory fluoroquinolone	169 (32.1)
Third cephalosporin	53 (10.1)
Cefepime	35 (6.7)
Aminoglycoside	13 (2.5)
Glycopeptide	79 (15.0)
Carbapenem	107 (20.3)
Colistin	8 (1.5)
Marcrolide	5 (1.0)
Others	44 (8.4)
Combination therapy of empirical antibiotics	249 (47.3)
Appropriateness of initial empiric antibiotics*	
Appropriate	102 (48.3)
Inappropriate	92 (43.6)
Not applicable	17 (8.1)
Changed antibiotics according to microbiologic results*	135 (64.0)

Ko, R. E., et al. (2021)

Outcome of Inappropriate Empiric Therapy

Multidrug resistance, inappropriate empiric therapy, and hospital mortality in Acinetobacter baumannii pneumonia and sepsis

MDR-AB → Inappropriate empiric therapy(IET)

13.4% vs. 73.9% (PSM)
OR = 5.5 (3.6-8.4), p<0.001

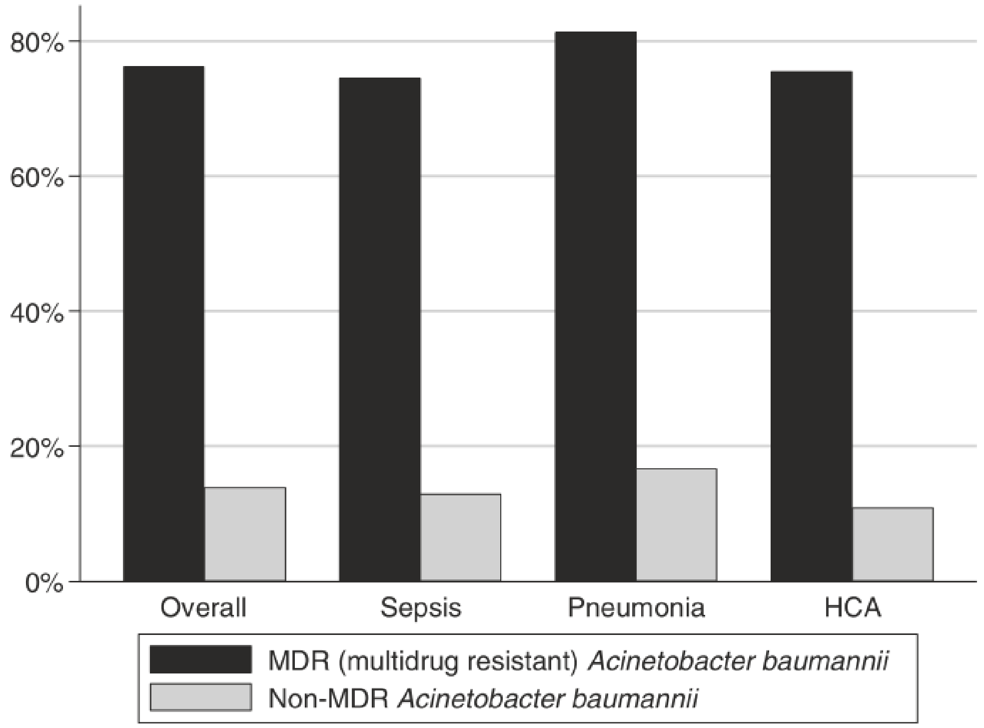


Fig. 1 Inappropriate empiric therapy as a function of multidrug resistance (MDR). *HCA* healthcare-associated

Inappropriate empiric therapy(IET) → Mortality

15.0% vs. 27.8% (PSM)
OR = 1.85 (1.35-2.54), p<0.001

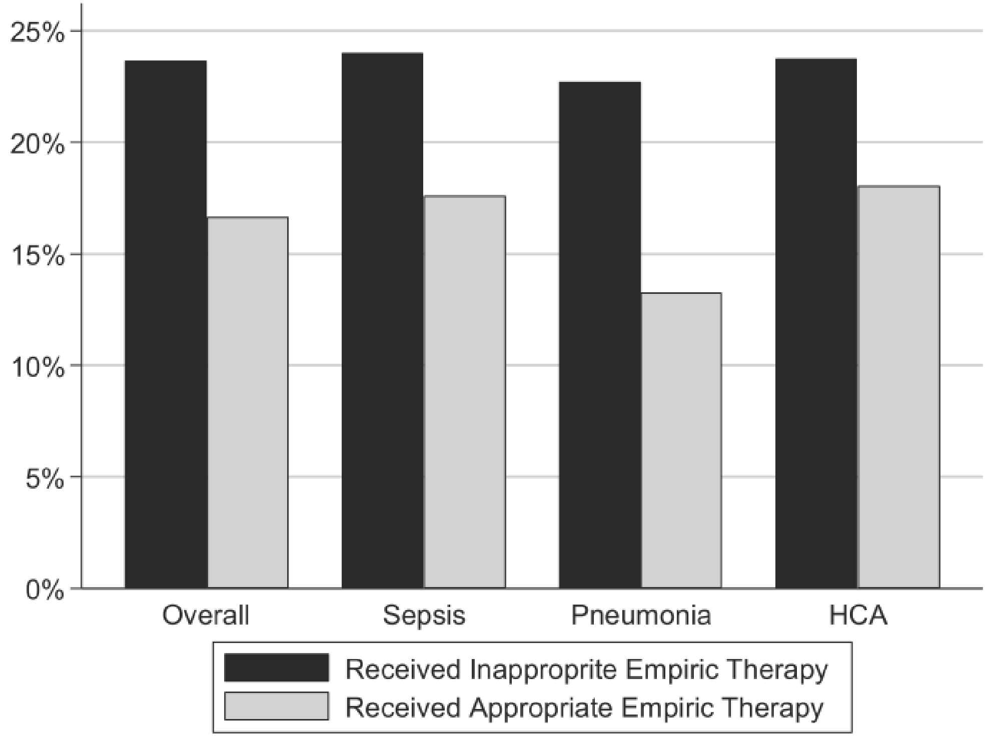


Fig. 2 Mortality and inappropriate empiric therapy. *HCA* healthcare-associated

Zilberberg, M. D., et al. (2016)

Outcome of Inappropriate Empiric Therapy

Carbapenem resistance, inappropriate empiric treatment, and outcomes among patients hospitalized with Enterobacteriaceae UTI, pneumonia and sepsis

CRE → Inappropriate empiric therapy(IET)

13.1% vs. 55.8% (PSM)
RR = 4.27 (3.64-5.00), p<0.001

Inappropriate empiric therapy(IET) → Mortality

10.5% vs. 11.9% (PSM)
OR = 1.13 (1.01-1.27), p<0.001

Inappropriate empiric therapy(IET) → LOS

9.6 vs. 14.6 days (PSM)
Excess days = 5.0 (4.4-5.6), p<0.001

Inappropriate empiric therapy(IET) → Costs

$22,005 vs. $32,837 (PSM)
Excess costs= $10,831 (9,254-12,409), p<0.001

Zilberberg, M. D., et al. (2017)

Outcome of Inappropriate Empiric Therapy

Inappropriate Empiric Therapy Impacts Complications and Hospital Resource Utilization Differentially Among Different Types of Bacterial Nosocomial Pneumonia:
A Multicenter Retrospective Cohort Study, United States, 2014–2019

Impact of Inappropriate Empiric Therapy on the Outcomes Stratified by Pneumonia Type

Outcome	Nonventilated Hospital-Acquired Bacterial Pneumonia Point Estimate (95% CI)	p	Ventilated Hospital-Acquired Bacterial Pneumonia Point Estimate (95% CI)	p	Ventilator-Associated Bacterial Pneumonia Point Estimate (95% CI)	p
Postinfection onset hospital LOS, d	4.9 (3.0–6.9)	< 0.001	0.6 (−1.3 to 2.5)	0.559	1.5 (−0.2 to 3.2)	0.075
Postinfection onset ICU LOS, d	1.1 (0.1–2.2)	0.029	1.4 (0.0–2.9)	0.056	0.4 (−0.6 to 1.4)	0.406
Hospital costs, $	$13,147 (3,009–23,284)	< 0.001	$4,658 (−2,424 to 11,750)	0.198	$6,161 (928–11,394)	0.021
Postinfection onset mechanical ventilation duration, d			0.5 (−0.3 to 1.2)	0.259	0.8 (−0.2 to 1.9)	0.104
Clostridium difficile	OR = 1.25 (0.58–2.71)	0.566	OR = 1.70 (0.86–3.34)	0.125	OR = 0.95 (0.58–1.55)	0.824
Extubation failure			OR = 1.20 (0.84–1.72)	0.323	OR = 1.34 (1.05–1.71)	0.017
Reintubation[a]			OR = 1.11 (0.69–1.81)	0.66	OR = 1.61 (1.17–2.20)	0.003

Characteristic	n = 4,728	%	n = 4,561	%	n = 8,530	%	p
Empiric treatment appropriateness							
Non-IET	3,856	81.56	3,929	86.14	7,178	84.15	< 0.001
IET	403	8.52	254	5.57	615	7.21	
Indeterminate	469	9.92	378	8.29	737	8.64	

Zilberberg, M. D., et al. (2022)

Table 3. Adjusted Contribution of Inappropriate Empiric Treatment to Outcomes

Outcome	Point estimate	95% CI	*P* Value
Mortality, OR	1.11	(0.96–1.27)	.151
30-day readmission, OR	1.16	(0.97–1.39)	.109
Total hospital LOS, additional days	4.8	(2.5–7.1)	<.001
Postinfection-onset hospital LOS, additional days	2.3	(1.2–3.4)	<.001
Postinfection-onset ICU LOS, additional days	1.1	(0.4–1.8)	.001
Postinfection-onset MV duration, additional days[a]	0.6	(−0.1 to 1.3)	.079
Hospital costs, additional $	12,142	(3,272–21,013)	<.001

Zilberberg, M. D., et al. (2022)

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

Andre C. Kalil,[1,a] Mark L. Metersky,[2,a] Michael Klompas,[3,4] John Muscedere,[5] Daniel A. Sweeney,[6] Lucy B. Palmer,[7] Lena M. Napolitano,[8] Naomi P. O'Grady,[9] John G. Bartlett,[10] Jordi Carratalà,[11] Ali A. El Solh,[12] Santiago Ewig,[13] Paul D. Fey,[14] Thomas M. File Jr,[15] Marcos I. Restrepo,[16] Jason A. Roberts,[17,18] Grant W. Waterer,[19] Peggy Cruse,[20] Shandra L. Knight,[20] and Jan L. Brozek[21]

International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia

Guidelines for the management of hospital-acquired pneumonia (HAP)/ ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociación Latinoamericana del Tórax (ALAT)

Antoni Torres[1,16], Michael S. Niederman[2,16], Jean Chastre[3], Santiago Ewig[4], Patricia Fernandez-Vandellos[5], Hakan Hanberger[6], Marin Kollef[7], Gianluigi Li Bassi[1], Carlos M. Luna[8], Ignacio Martin-Loeches[9], J. Artur Paiva[10], Robert C. Read[11], David Rigau[12], Jean François Timsit[13], Tobias Welte[14] and Richard Wunderink[15]

2016-2017 USA vs. Europe guideline

2016 USA guideline

Table 2. Risk Factors for Multidrug-Resistant Pathogens

Risk factors for MDR VAP	
	Prior intravenous antibiotic use within 90 d
	Septic shock at time of VAP
	ARDS preceding VAP
	Five or more days of hospitalization prior to the occurrence of VAP
	Acute renal replacement therapy prior to VAP onset
Risk factors for MDR HAP	
	Prior intravenous antibiotic use within 90 d
Risk factors for MRSA VAP/HAP	
	Prior intravenous antibiotic use within 90 d , Prior detection of MRSA
Risk factors for MDR *Pseudomonas* VAP/HAP	
	Prior intravenous antibiotic use within 90 d , Structural lung disease (ie, bronchiectasis)

High risk of mortality in HAP
- Need for MV (vHAP)
- Septic shock

- All hospitals regularly generate and disseminate a **local antibiogram**, ideally one that is **specific to their HAP or ICU population**, if possible.
- **Empiric treatment regimens** be informed by the local distribution of pathogens associated with HAP/VAP and their antimicrobial susceptibilities.
- Update

Any of the following :
- a risk factor for antimicrobial resistance (Table 2.)
- in units where **>10%–20% of S. aureus are MRSA**
  > 10% of GNB are resistant to monotherapy
- in units where local antimicrobial susceptibility rates (or MDR prevalence) is not known

Goal : ≥ 95% of patient receiving appropriate empiric therapy

"…when implementing these recommendations, **individual ICUs** may elect to **modify these thresholds**…."

2016 IDSA/ATS guideline

VAP

Table 3. Suggested Empiric Treatment Options for Clinically Suspected Ventilator-Associated Pneumonia in Units Where Empiric Methicillin-Resistant *Staphylococcus aureus* Coverage and Double Antipseudomonal/Gram-Negative Coverage Are Appropriate

A. Gram-Positive Antibiotics With MRSA Activity	B. Gram-Negative Antibiotics With Antipseudomonal Activity: β-Lactam–Based Agents	C. Gram-Negative Antibiotics With Antipseudomonal Activity: Non-β-Lactam–Based Agents
Glycopeptides[a] Vancomycin 15 mg/kg IV q8–12h (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Antipseudomonal penicillins[b] Piperacillin-tazobactam 4.5 g IV q6h[b]	Fluoroquinolones Ciprofloxacin 400 mg IV q8h Levofloxacin 750 mg IV q24h
OR	OR	OR
Oxazolidinones Linezolid 600 mg IV q12h	Cephalosporins[b] Cefepime 2 g IV q8h Ceftazidime 2 g IV q8h	Aminoglycosides[a,c] Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h
	OR	OR
	Carbapenems[b] Imipenem 500 mg IV q6h[d] Meropenem 1 g IV q8h	Polymyxins[a,e] Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose) [135] Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses
	OR	**reserved for settings with high prevalence of MDR** and local expertise in using this medication
	Monobactams[f] Aztreonam 2 g IV q8h	

Anti-MRSA antibiotics

Anti-MSSA & Pseudomonal antibiotics

Anti-Pseudomonal antibiotics

If structural lung disease (ie, bronchiectasis) : dual anti-pseudomonal coverage

Single anti-Pseudo(&MSSA) → Dual anti-Pseudo(&MSSA) → Triple (Dual anti-Pseudo + anti-MRSA)

HAP

Table 4. Recommended Initial Empiric Antibiotic Therapy for Hospital-Acquired Pneumonia (Non-Ventilator-Associated Pneumonia)

Need for MV (vHAP), Septic shock

Not at High Risk of Mortality[a] and no Factors Increasing the Likelihood of MRSA[b,c]	Not at High Risk of Mortality[a] but With Factors Increasing the Likelihood of MRSA[b,c]	High Risk of Mortality or Receipt of Intravenous Antibiotics During the Prior 90 d[a,c]
One of the following:	One of the following:	Two of the following, avoid 2 β-lactams:
Piperacillin-tazobactam[d] 4.5 g IV q6h	Piperacillin-tazobactam[d] 4.5 g IV q6h	Piperacillin-tazobactam[d] 4.5 g IV q6h
OR	OR	OR
Cefepime[d] 2 g IV q8h	Cefepime[d] or ceftazidime[d] 2 g IV q8h	Cefepime[d] or ceftazidime[d] 2 g IV q8h
OR	OR	OR
Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily	Levofloxacin 750 mg IV daily
	Ciprofloxacin 400 mg IV q8h	Ciprofloxacin 400 mg IV q8h
	OR	OR
Imipenem[d] 500 mg IV q6h	Imipenem[d] 500 mg IV q6h	Imipenem[d] 500 mg IV q6h
Meropenem[d] 1 g IV q8h	Meropenem[d] 1 g IV q8h	Meropenem[d] 1 g IV q8h
	OR	OR
	Aztreonam 2 g IV q8h	Amikacin 15–20 mg/kg IV daily
		Gentamicin 5–7 mg/kg IV daily
		Tobramycin 5–7 mg/kg IV daily
		OR
		Aztreonam[e] 2 g IV q8h
	Plus:	Plus:
	Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg IV × 1 for severe illness)
	OR	OR
	Linezolid 600 mg IV q12h	Linezolid 600 mg IV q12h
		If MRSA coverage is not going to be used, include coverage for MSSA. Options include: Piperacillin-tazobactam, cefepime, levofloxacin, imipenem, meropenem. Oxacillin, nafcillin, and cefazolin are preferred for the treatment of proven MSSA, but would ordinarily not be used in an empiric regimen for HAP.
If patient has severe penicillin allergy and aztreonam is going to be used instead of any β-lactam–based antibiotic, include coverage for MSSA.		

Anti-MSSA & Pseudomonal antibiotics

Colistin (x)

Antibiotics(90d), MRSA > 20%, colonization

Anti-MRSA antibiotics

Single anti-Pseudo(&MSSA) → Dual (anti-Pseudo+ anti-MRSA) → Triple (Dual anti-Pseudo + anti-MRSA)

2017 Europe guideline

HAP/VAP
: assess risk for MDR pathogens and mortality

(Early onset & Low MDR background)

Low MDR pathogen risk and low mortality risk#

Antibiotic monotherapy: Narrow-spectrum agents against non-resistant GNB and MSSA

Ertapenem, ceftriaxone, cefotaxime, moxifloxacin or levofloxacin

(Late onset, and/or High MDR or Acinetobacter background)

High MDR pathogen risk and/or >15% mortality risk

No septic shock

Single Gram-negative anti-pseudomonal agent [if active for >90% GNB] **± MRSA therapy(>25%)**

Imipenem, meropenem, cefepime, pip/tazo, levofloxacin or ceftazidime

Early or Late onset
Septic shock

Broad-spectrum agents targeting **PA**, **AB** and **ESBL-PE**

: Dual Gram-negative, anti-pseudomonal coverage (beta-lactam plus AG/FQ/AB:Colistin) ± MRSA therapy(>25%)

Imipenem, meropenem, cefepime, pip/tazo, aztreonam or ceftazidime

2017 ERS/ESCIM/ESCMID/ALAT guideline

2012-2015 US

Potential Impact of Hospital-acquired Pneumonia Guidelines on Empiric Antibiotics

An Evaluation of 113 Veterans Affairs Medical Centers

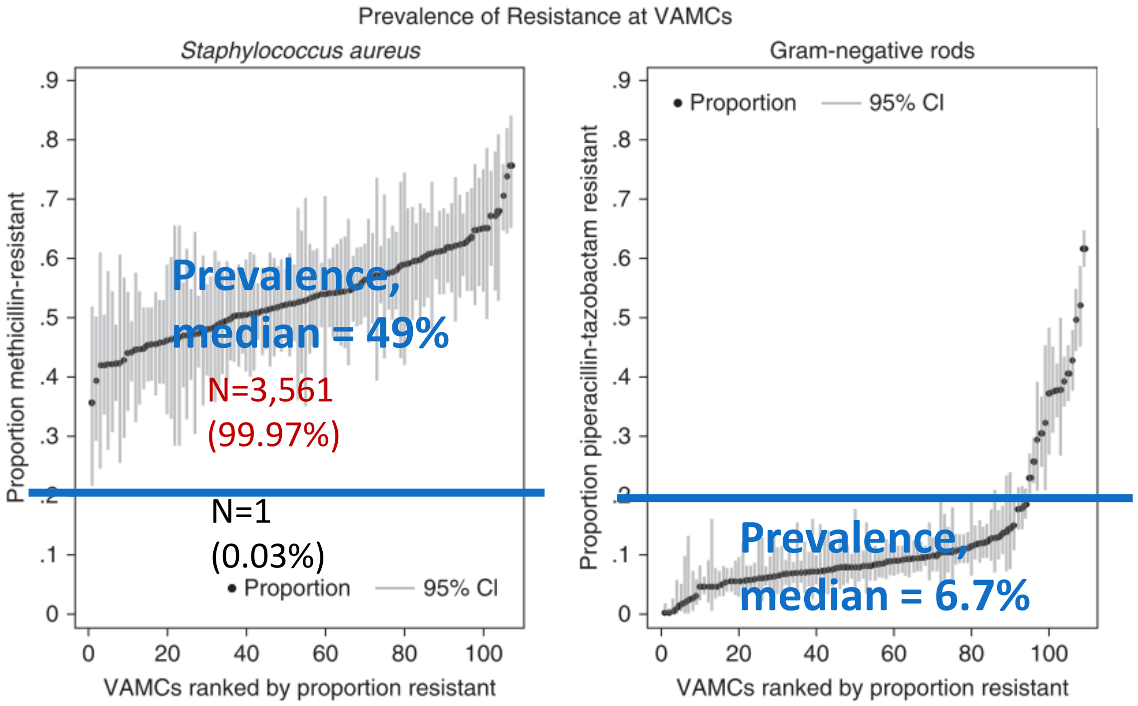


Table 2. Multivariable model for resistant infection in hospital-acquired pneumonia

	Odds Ratio (95% CI)	*P* Value
Variables for MRSA resistance		
20% threshold	Undefined*	*
IV antibiotics in last 90 d	1.98 (1.03–3.81)	0.04
Pressor order	3.89 (1.17–12.91)	0.03
Mechanical ventilation	1.82 (0.43–7.67)	0.41
	AUC = 0.55	
Variables for GNR resistance		
IV antibiotics in last 90 d	1.00 (0.44–2.28)	0.99
Pressor order	1.33 (0.18–9.86)	0.78
Mechanical ventilation	4.37 (1.52–12.57)	0.01
	AUC = 0.55	

N=3,562
MRSA (184, 5.17%), R-GNR (82, 2.3%)

N=1199 (proven microbes, 33.66%)
MRSA (184, 15.3%), R-GNR (82, 6.8%)

IDSA CPG's Empiric MRSA guidance (20% threshold)
: sensitivity 100%, specificity 0.03%
→ **94.81% potentially overtreated using 20% threshold**

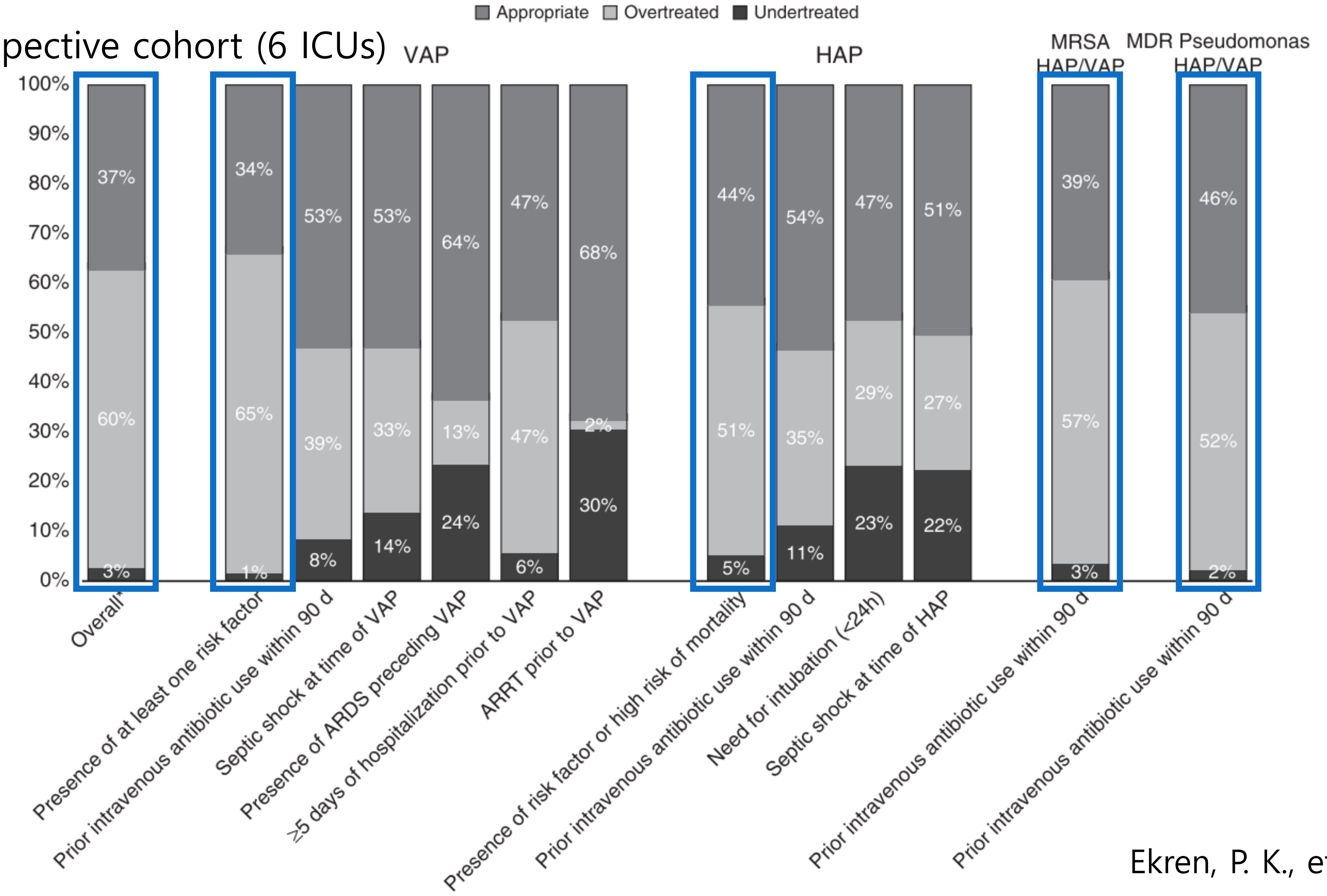
Bostwick, A. D., et al. (2019)

Evaluation of the 2016 Infectious Diseases Society of America/American Thoracic Society Guideline Criteria for Risk of Multidrug-Resistant Pathogens in Patients with Hospital-acquired and Ventilator-associated Pneumonia in the ICU

In a single center prospective cohort (6 ICUs)

Overtreated > Appropriate > Undertreated

High sensitivity, Low specificity, Very Low PPV for MRSA



Ekren, P. K., et al. (2018)

Carbapenem-based empiric regimen

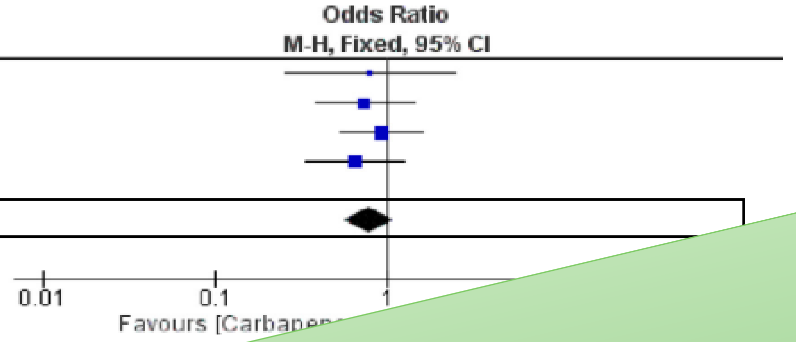
Carbapenems vs. alternative β-lactams for the treatment of nosocomial pneumonia: A systematic review and meta-analysis

Mortality

OR 0.79 (0.57-1.11)

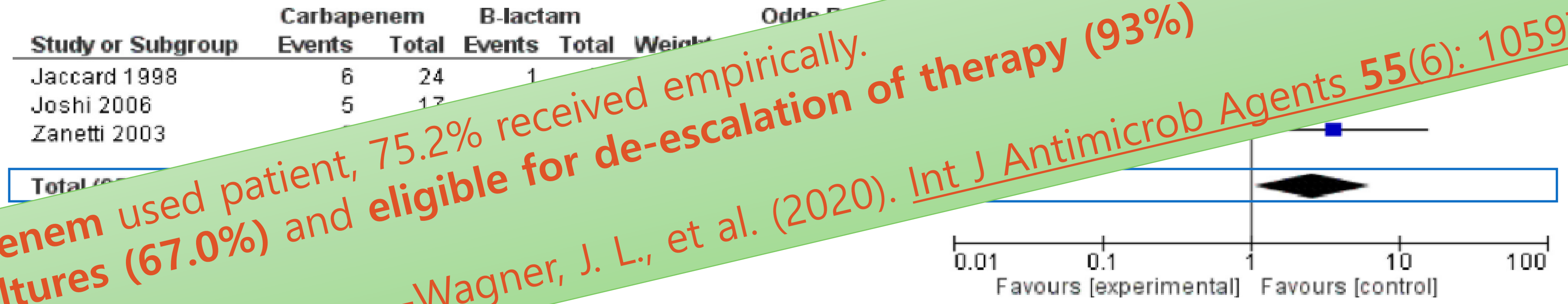
Study or Subgroup	Carbapenem Events	Carbapenem Total	Alternate β-lactam Events	Alternate β-lactam Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Jaccard 1998	6	79	7	75	8.7%	0.80 [0.26, 2.49]
Joshi 2006	17	215	23	222	27.3%	0.74 [0.39, 1.43]
Rea-Nato 2008	30	217	31	212	35.3%	0.94 [0.54, 1.61]
Zanetti 2003	19	101	28	108	28.7%	0.66 [0.34, 1.28]
Total (95% CI)		**612**		**617**	**100.0%**	**0.79 [0.57, 1.11]**
Total events	72		89			

Heterogeneity: Chi² = 0.69, df = 3 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.35 (P = 0.18)



Development of resistance in Pseudomonas

OR 2.64 (1.08-6.44)



Of the **carbapenem** used patient, 75.2% received empirically.
\- **negative cultures (67.0%)** and **eligible for de-escalation of therapy (93%)**

-Wagner, J. L., et al. (2020). Int J Antimicrob Agents **55**(6): 105970.

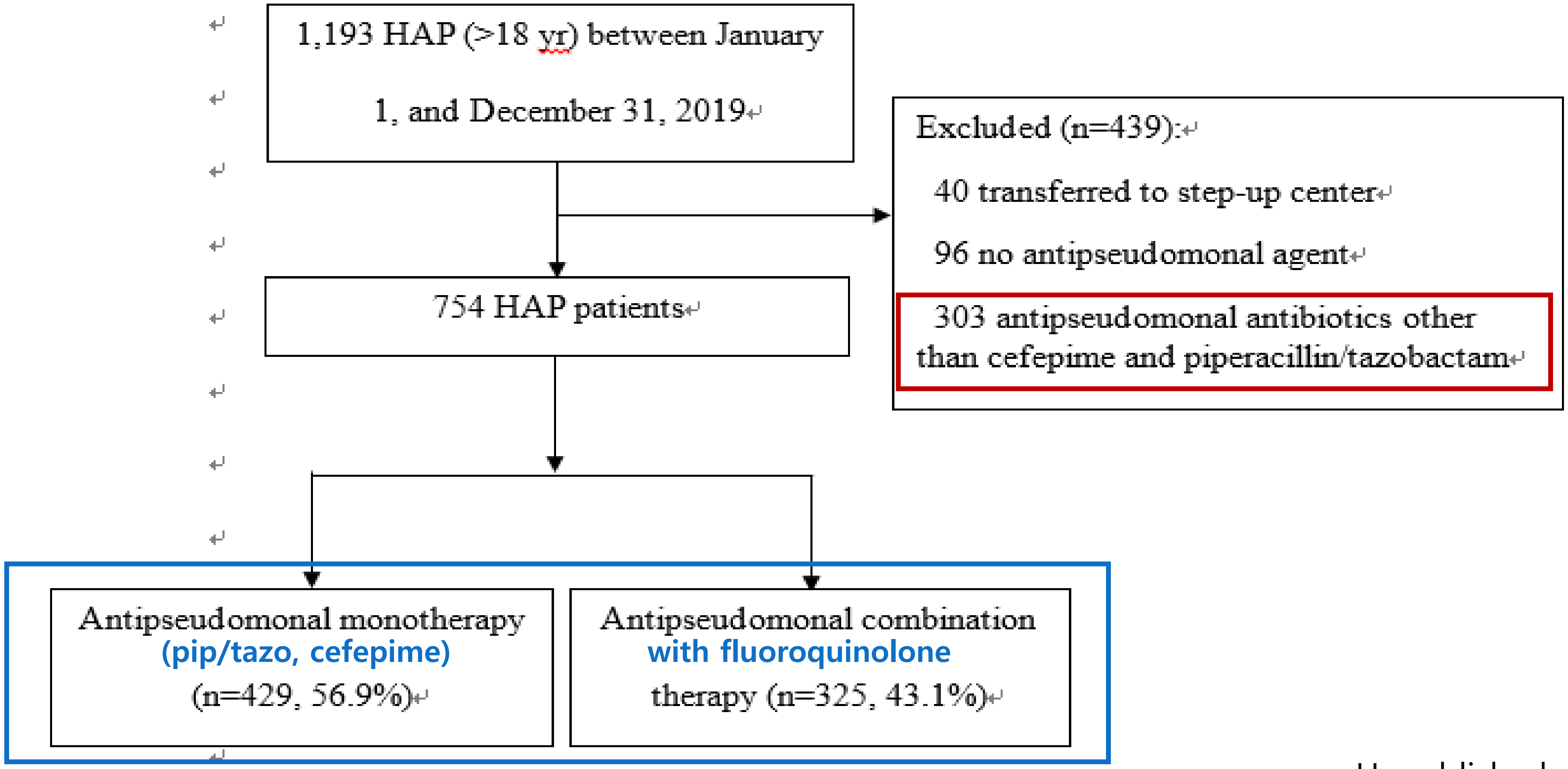
...usions: No differences in clinical outcomes were observed between carbapenems and non-carbapenem β-lactams in nosocomial pneumonias. Those infected with *P. aeruginosa* fared worse and were more likely to have resistance develop if they were treated with imipenem. Additional studies are warranted.

O'Donnell, J. N., et al. (2018)

2019 (16 hospitals, Korea)

Dual anti-Pseudomonal empiric combination

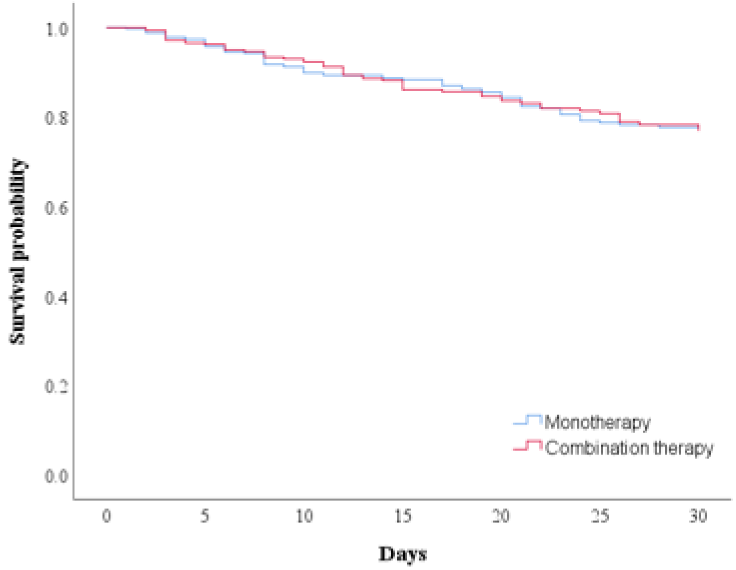
Figure 1. Flowchart. HAP, hospital-acquired pneumonia.



Unpublished data

Fig. 2. Kaplan-Meier curve analysis for 30-day mortality

A. Before PS matching in overall cohort (Log Rank p=0.955)



B. After PS matching in overall cohort (Log Rank p=0.820)

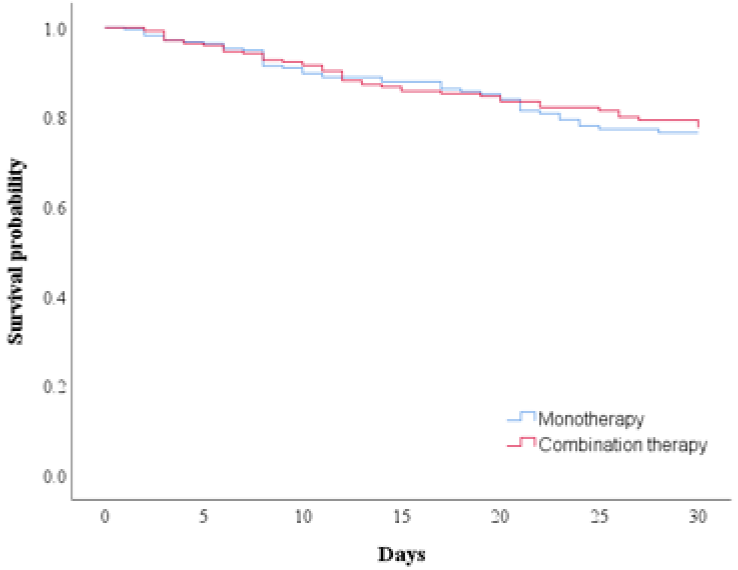


Table 4. Odds ratios for 30-day mortality in PS matched cohort

Variables	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
Overall				
Monotherapy	1 (Reference)		1 (Reference)	
Combination therapy	1.051 (0.678–1.631)	0.823	1.075 (0.664–1.739)	0.769
Microbiologically documented				
Monotherapy	1 (Reference)		1 (Reference)	
Combination therapy	1.562 (0.729–3.349)	0.251	1.082 (0.460–2.549)	0.856
Clinically documented				
Monotherapy	1 (Reference)		1 (Reference)	
Combination therapy	0.771 (0.409–1.464)	0.422	0.954 (0.485–1.879)	0.892

PS: propensity score; OR: odds ratio; CI: confidence interval.

Unpublished data

Appropriate Empiric Combination therapy for Pseudomonas aeruginosa

Outcomes of Appropriate Empiric Combination versus Monotherapy for *Pseudomonas aeruginosa* Bacteremia

TABLE 2 Risk factor analysis of 30-day mortality

	Univariate analysis		Multivariate analysis	
Variable	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.01 (0.99–1.03)	0.24		
Male gender	1.28 (0.77–2.13)	0.34		
Combination therapy	1.14 (0.63–2.04)	0.67		
Length of stay prior to culture	1.01 (1.00–1.01)	0.01	1.01 (1.00–1.02)	0.01
Infection-related APACHE II score	1.10 (1.07–1.15)	<0.01	1.12 (1.08–1.17)	<0.01
Comorbidities				
Cardiovascular conditions	0.41 (0.23–0.73)	<0.01		
Respiratory conditions	1.46 (0.73–2.94)	0.29		
Central nervous system disease	0.63 (0.27–1.48)	0.29		
Renal disease	1.21 (0.72–2.03)	0.48		
Diabetes mellitus	1.51 (0.85–2.67)	0.16		
Immunosuppression	0.80 (0.45–1.42)	0.44		
Liver disease	2.09 (1.05–4.14)	0.04		

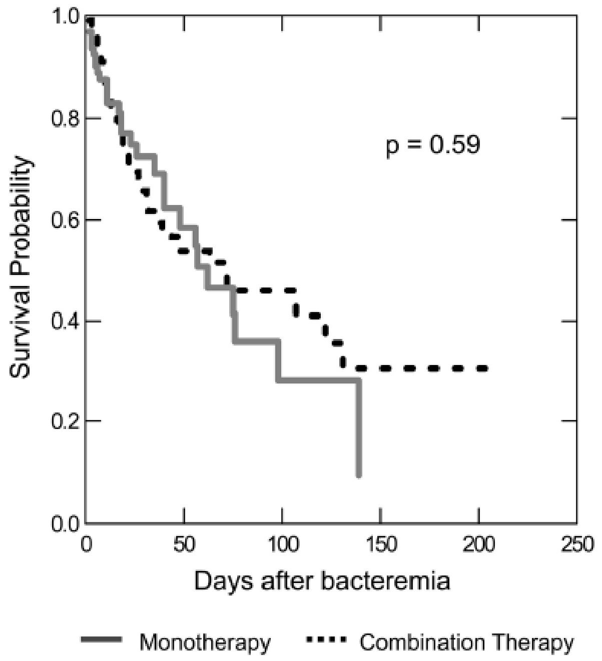
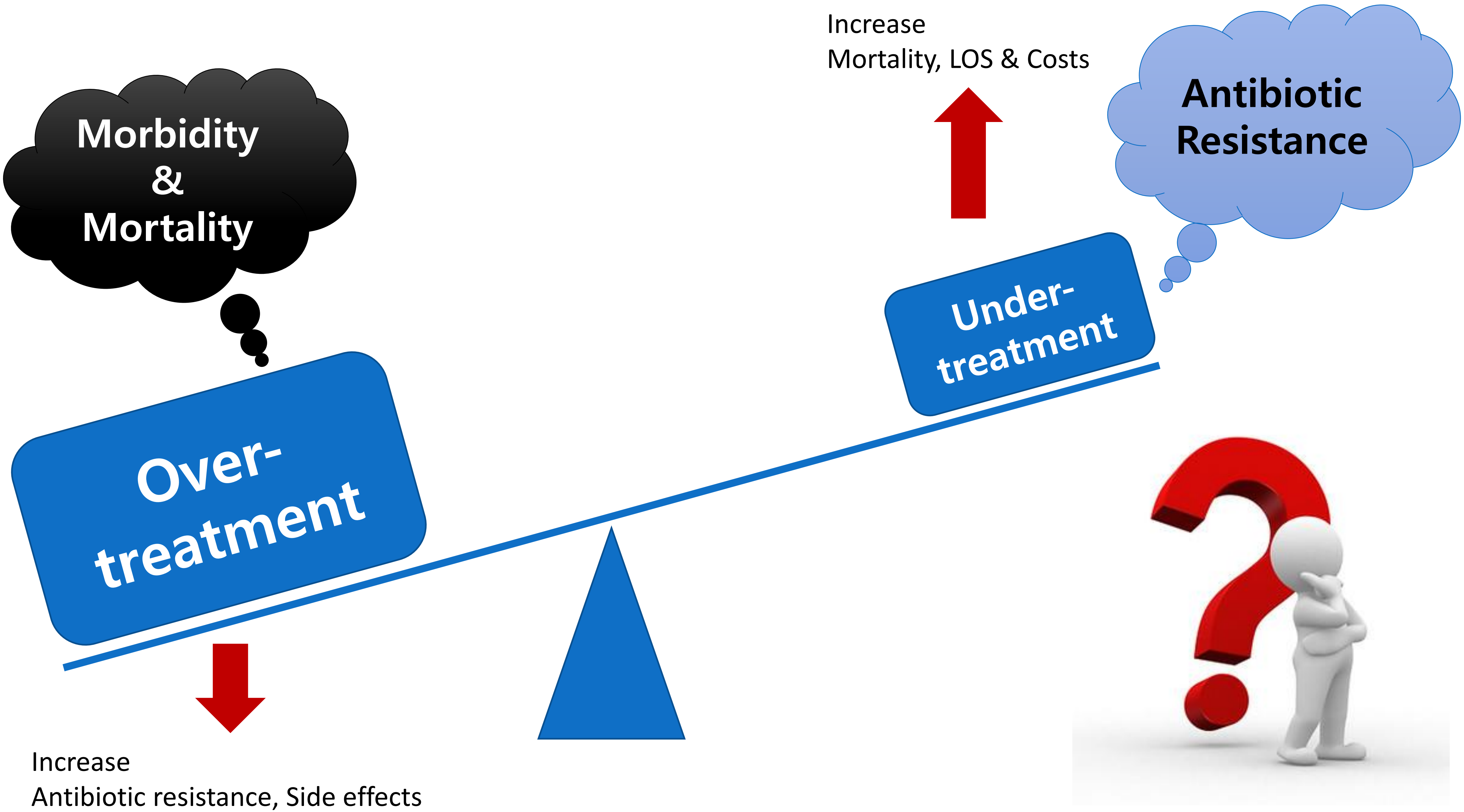


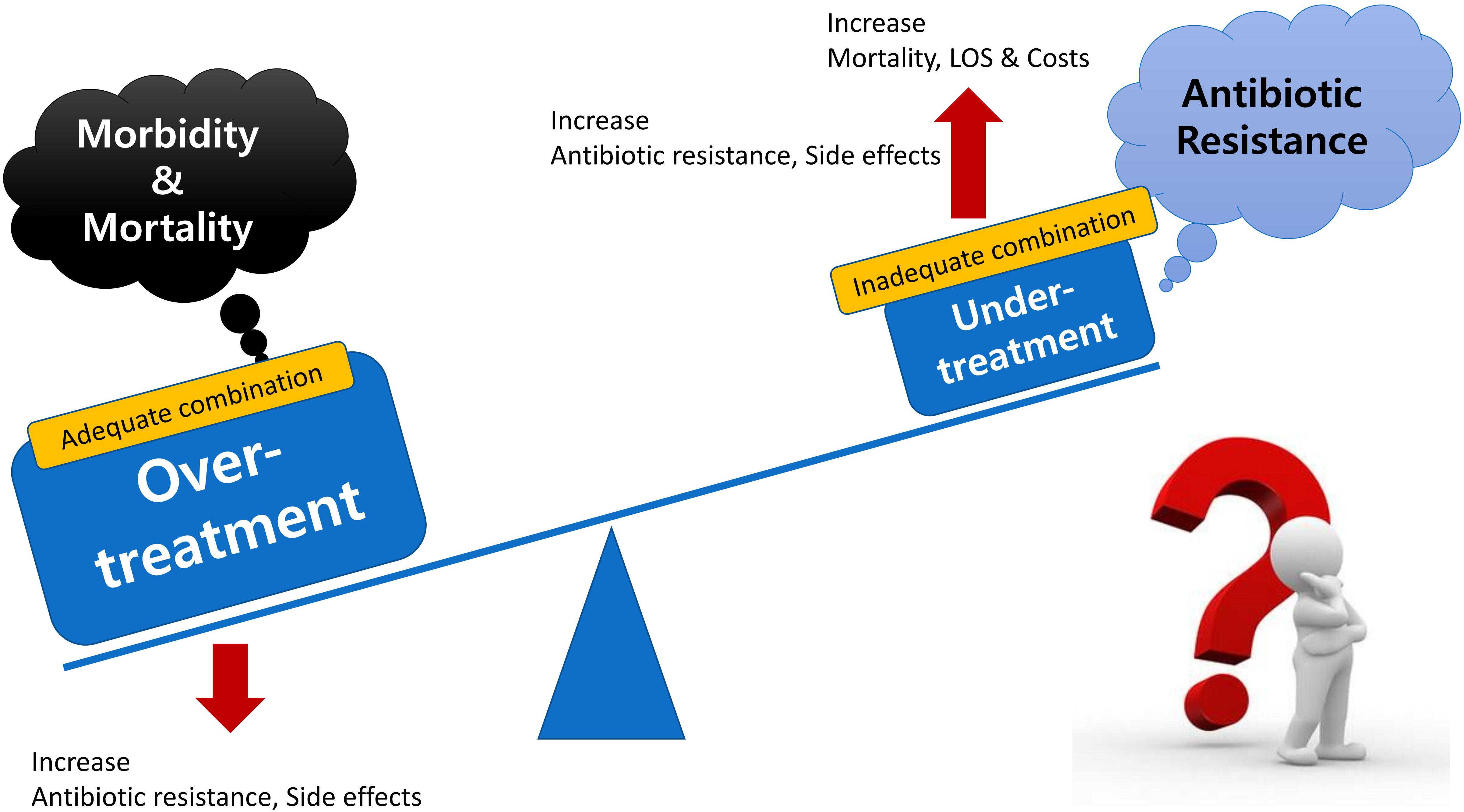
FIG 1 Comparison of times to mortality.

Empirical combination therapy did not offer an additional benefit, as long as the isolate was susceptible to at least one agent.

Inappropriate vs. Appropriate empiric therapy (30-d mortality **43.8% vs. 21.5%**, *P*=0.03)

Antimicrob Agents Chemother. 2013 Mar;57(3):1270-4.


Morbidity
&
Mortality
Increase
Mortality, LOS & Costs
Antibiotic
Resistance
Under-
treatment
Over-
treatment
Increase
Antibiotic resistance, Side effects


Morbidity
&
Mortality
Increase
Mortality, LOS & Costs
Increase
Antibiotic resistance, Side effects
Antibiotic
Resistance
Inadequate combination
Under-
treatment
Adequate combination
Over-
treatment
Increase
Antibiotic resistance, Side effects

Consideration for the initial empiric antibiotics

- Severity of illness (Mortality risk)

-Organ failure, Shock

-HAP (NV-HAP, V-HAP), VAP ?

- Individual clinical factors
- Immune status
- Potential pathogen
- MDRO risk

(Hospital days, Antibiotic exposure, etc.)

- Local ecology of MDRO
- Colonization of MDRO
- Benefit vs. Harm

Narrow vs. Broad spectrum

G(-) vs. G(+) coverage

Anti-Pseudomonal coverage

Anti-ESBL-PE coverage

Anti-MRSA coverage

Anti-Carbapenem-R coverage

Single vs. Dual vs. Triple

Local ecology vs. Colonization

Non-toxic vs. Toxic drugs

Old vs. New drugs

Bolus vs. Prolonged infusion

Risk factors for MDRO-related infection

Table 2 Principal variables associated with resistance for main MDROs causing NP

MDRO	Risk factors	References
MRSA	⇒ Age ⇒ NP appearance > 6 days after admittance ⇒ NP development excluding summers ⇒ Respiratory diseases ⇒ Multilobar involvement ⇒ Respiratory infection/colonization caused by MRSA in the previous year ⇒ Hospitalization in the previous 90 days ⇒ Recent nursing home or hospital stay ⇒ Recent exposure to fluoroquinolone or antibiotics treating Gram-positive organisms	[61–63]
Pseudomonas aeruginosa	⇒ Prior airway colonization by *P. aeruginosa* ⇒ Previous antibiotic treatment ⇒ Solid cancer ⇒ Shock ⇒ Alcohol abuse ⇒ Pleural effusion ⇒ Chronic liver disease independently predicted MDR amongst Pa-ICUAP ⇒ Prior use of carbapenems ⇒ Prior use of fluoroquinolones ⇒ Duration of therapy ⇒ APACHE II score	[64, 65]
KPC	⇒ Admission to ICU, antimicrobial use ⇒ Prior carbapenem ⇒ Invasive operation ⇒ Previous non-KPC-Kp infections ⇒ Duration of previous antibiotic therapy before KPC colonization	[66–69]
Enterobacteriaceae	⇒ Male sex ⇒ Admission from another health care facility ⇒ Ventilation at any point before culture during the index hospitalization ⇒ Receipt of any carbapenem in the prior 30 days ⇒ Receipt of any anti-MRSA agent in the prior 30 days	[68, 70]
Acinetobacter baumannii	⇒ APACHE II score at admission ⇒ Systemic illnesses (chronic respiratory disease and cerebrovascular accident) ⇒ Presence of excess non-invasive or invasive devices (mechanical ventilation) ⇒ Ever used antibiotics within 28 days (carbapenem and cefepime)	[5, 71, 72]

KPC Klebsiella pneumoniae carbapenemase, *MRSA* meticillin-resistant *Staphylococcus aureus*, *MDRO* multidrug-resistant organism, *NP* nosocomial pneumonia

Zaragoza, R., et al. (2020)

Risk factors for MDRO-related infection

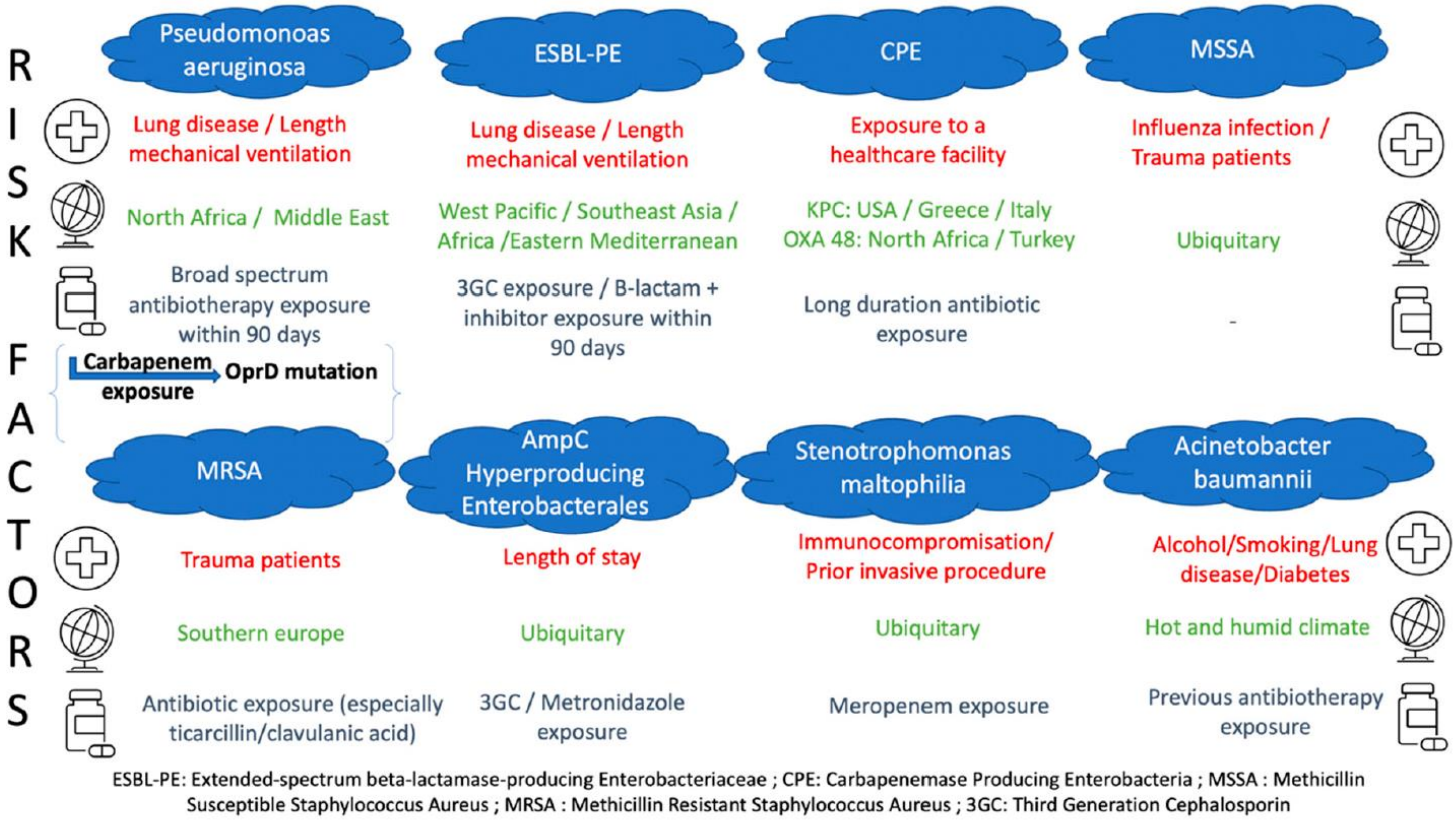


Figure 2. Risk factors for MDRO-related infections.

Antibiotics **2022**, *11*, 359.

Risk factors for MRSA HAP/VAP

Table 2. Risk Factors for Multidrug-Resistant Pathogens

Risk factors for MDR VAP
Prior intravenous antibiotic use within 90 d
Septic shock at time of VAP
ARDS preceding VAP
Five or more days of hospitalization prior to the occurrence of VAP
Acute renal replacement therapy prior to VAP onset
Risk factors for MDR HAP
Prior intravenous antibiotic use within 90 d
Risk factors for MRSA VAP/HAP
Prior intravenous antibiotic use within 90 d
Risk factors for MDR *Pseudomonas* VAP/HAP
Prior intravenous antibiotic use within 90 d

2016 IDSA/ATS guideline

Guideline-induced MRSA overtreatment

NPV 91%, **PPV 8%** → **anti-MRSA overtreatment**

Ekren, P. K., et al. (2018)

Clinical predictors of methicillin-resistant *Staphylococcus aureus* in nosocomial and healthcare-associated pneumonia: a multicenter, matched case–control study Parente, D. M., et al. (2018)

- **Respiratory colonization/infection of MRSA in the previous 12 months** **OR 14.81** (CI 4.13-53.13), p<0.001
- Hospitalization in the last 90 days **OR 2.41** (CI 1.21- 4.81), p=0.012
- Age **OR 1.02** (CI 1.001-1.05), p=0.040

The Clinical Utility of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Nasal Screening to Rule Out MRSA Pneumonia: A Diagnostic Meta-analysis With Antimicrobial Stewardship Implications

MRSA nasal surveillance screening using either culture or PCR

Table 2. Performance Characteristics of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Surveillance Screening by MRSA Pneumonia Type

Type of Pneumonia	Studies, No.	Sensitivity (95% CI), %	Specificity (95% CI), %	Positive LR (95% CI)	Negative LR (95% CI)	DOR (95% CI)	PPV, %	NPV, %
All	22	70.9 (58.8–80.6)	90.3 (86.1–93.3)	7.28 (5.3–10.1)	0.32 (0.22–0.46)	24.6 (13.6–37.5)	44.8	96.5
CAP/HCAP	4	85.0 (59.7–95.6)	92.1 (81.5–96.9)	10.8 (5.1–23.0)	0.16 (0.06–0.48)	66.4 (28.5–154.6)	56.8	98.1
VAP	5	40.3 (17.4–68.4)	93.7 (77.1–98.4)	6.34 (1.94–20.8)	0.63 (0.42–0.98)	9.96 (2.63–37.6)	35.7	94.8

Parente, D. M., et al. (2018)

Diagnostic accuracy of Gram staining when predicting staphylococcal hospital-acquired pneumonia and ventilator-associated pneumonia: a systematic review and meta-analysis

Gram stain morphology by high quality LRT sample at pneumonia diagnosis
- sputum, endotracheal aspirates, BAL

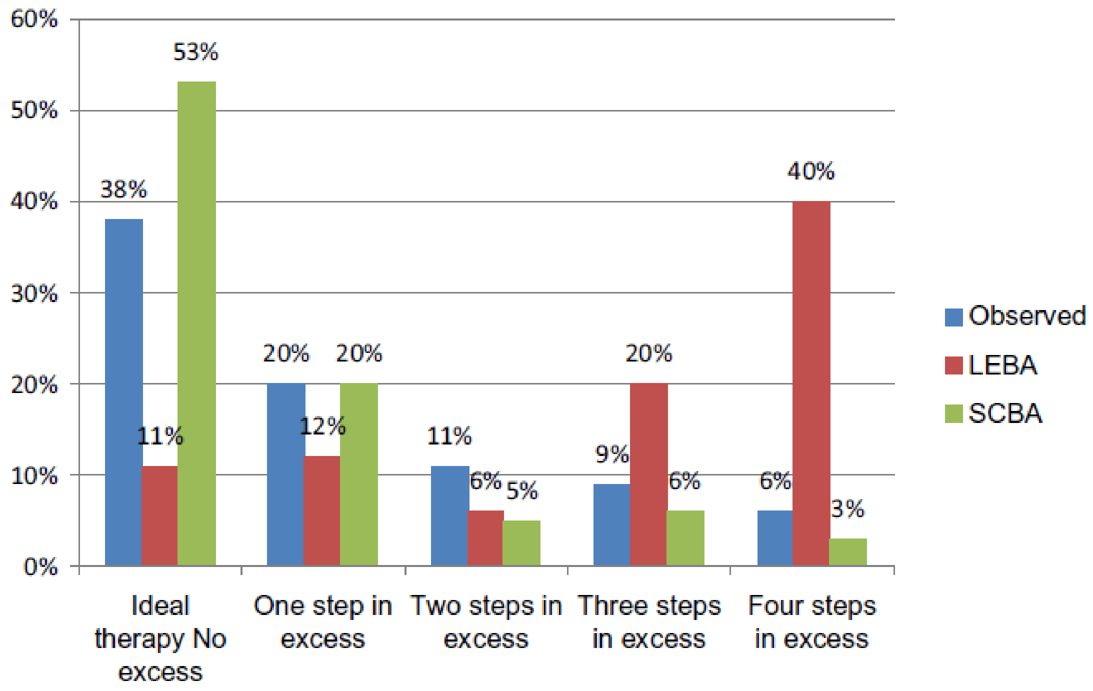
Diagnostic accuracy of Gram staining with presence of Gram-positive cocci in clusters, as compared with a positive final culture of *Staphylococcus aureus*

Gram staining	Prevalence of *S. aureus*	Agreement (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	LR+ (95%CI)	LR-(95%CI)	Diagnostic odds ratio (95%CI)
Overall ($n = 366$)	15%	90% (87–93)	43% (29–57)	98% (96–100)	82% (63–94)	91% (87–94)	26.58 (10.56–66.89)	0.58 (0.46–0.73)	45.6 (16.2–128.3)
Pneumonia type									
HAP ($n = 127$)	9%	93% (87–97)	42% (15–72)	98% (94–100)	71% (29–96)	94% (88–98)	23.96 (5.20–110.45)	0.59 (0.37–0.96)	40.4 (6.6–246.3)
VAP ($n = 239$)	18%	88% (84–92)	43% (28–59)	99% (96–100)	86% (64–97)	89% (84–93)	28.14 (8.68–91.22)	0.58 (0.45–0.75)	48.5 (13.3–176.9)
Sampling method									
Non-invasive sampling ($n = 307$)	15%	90% (86–93)	39% (25–55)	99% (96–100)	82% (60–95)	90% (86–93)	25.53 (9.05–72.03)	0.62 (0.49–0.78)	41.3 (13.1–130.6)
Invasive sampling ($n = 59$)	14%	94% (86–98)	63% (25–92)	98% (90–100)	83% (36–100)	94% (84–100)	31.88 (4.26–238.73)	0.38 (0.16–0.94)	83.3 (7.2–958.7)

Ranzani, O. T., et al. (2020)

Local Ecology vs. Surveillance Culture(Colonization)

Development of antibiotic treatment algorithms based on local ecology and respiratory surveillance cultures to restrict the use of broad-spectrum antimicrobial drugs in the treatment of hospital-acquired pneumonia in the intensive care unit: a retrospective analysis



Appropriateness and spectrum of antimicrobial therapy

Appropriate antibiotic therapy was prescribed in 95 (84.1%) HAP episodes. Antimicrobial choices proposed by LEBA and SCBA were appropriate in 88.5% and 87.6%, respectively. Paired analysis showed no significant difference in adequacy for the different strategies (prescribed therapy versus LEBA: $P = 0.33$; prescribed therapy versus SCBA: $P = 0.5$; LEBA versus SCBA: $P = 0.99$). Pathogens associated with inadequate empirical therapy are detailed in Table 3.

In significantly more episodes, SCBA proposed antibiotics of a narrower spectrum as compared to both the prescribed therapy and the regimen suggested by LEBA ($P < 0.001$) (Figure 3). Significantly less combination therapy was proposed by SCBA (7.1%) in comparison with LEBA (81.4%) ($P < 0.001$). SCBA recommended carbapenems in significantly fewer episodes than LEBA (24 (21.2%) versus 92 (81.4%), respectively ($P < 0.001$)).

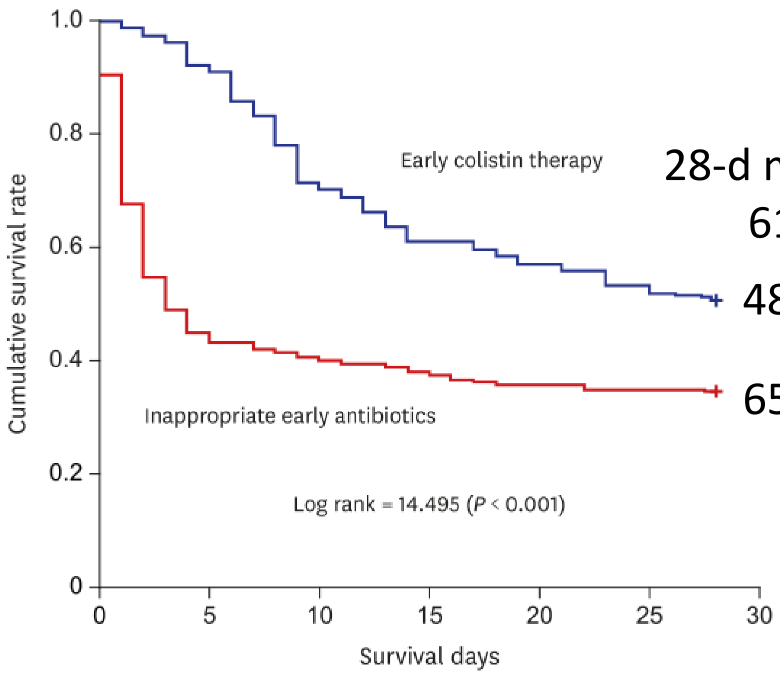
Conclusion: Rates of appropriate antimicrobial coverage were identical in LEBA and SCBA. However, in this setting of moderate MDR prevalence, the use of SCBA would result in a significant reduction of the use of broad-spectrum drugs and may be a preferential strategy when implementing antibiotic stewardship programs.

De Bus *et al. Critical Care* 2014, **18**:R152

Empiric Colistin therapy for CRAB

Early Intravenous Colistin Therapy as a Favorable Prognostic Factor for 28-day Mortality in Patients with CRAB Bacteremia: a Multicenter Propensity Score-Matching Analysis

Clinical characteristics	Before propensity score-matching			After propensity score-matching		
	Early colistin therapy (n = 76)	Inappropriate early antibiotics (n = 227)	*P* value	Early colistin therapy (n = 45)	Inappropriate early antibiotics (n = 45)	*P* value
Source of bacteremia						
Pneumonia	41 (53.9)	102 (44.9)	0.19	26 (57.8)	24 (53.3)	0.83
Catheter-related infection	9 (11.8)	19 (8.4)	0.37	3 (6.7)	5 (11.1)	0.71
Intraabdominal infection	2 (2.6)	13 (5.7)	0.37	1 (2.2)	1 (2.2)	> 0.99
Unknown	19 (25.0)	80 (35.2)	0.12	14 (31.1)	13 (28.9)	> 0.99



28-d mortality
61.4%
48.7%
65.6%

<Prognostic factors of 28-d mortality (after PSM)>

- **Vasopressor** : **OR 8.20** (2.50-26.85), p=0.01
- Previous CRAB colonization within a month before blood culture : OR 4.75 (1.52-14.81), p=0.01
- Previous Fluoroquinolones at the time of blood culture : OR 3.25 (1.02-10.41), p=0.047
- **Early Colistin therapy** : **OR 0.31** (0.11-0.88), p=0.03
- AKI during treatment after blood culture : OR 1.24 (0.86-1.80), p=0.27

<Prognostic factors of 14-d mortality>

- SOFA score ≥8 : OR 4.88 (2.41-9.87), p<0.001
- Vasopressor : OR 3.94 (1.83-8.47), p<001
- **Pneumonia** : **OR 2.05** (1.05-4.02), p=0.040
- **Early Colistin therapy** : **OR 0.32** (0.15-0.69), p=0.003
- **AKI during treatment** after blood culture : **OR 2.31** (1.15-4.63), p=0.020

Kim, T., et al. (2019).

Empiric Combination therapy for CRAB

Survival of carbapenem-resistant Acinetobacter baumannii bacteremia: Colistin monotherapy vs. Colistin plus meropenem

Patient characteristics	Colistin (n = 40)	Colistin plus meropenem (n = 31)	*p*
Type of infection			
Pneumonia	15 (37.5)	16 (51.6)	0.33
CRI	17 (42.5%)	10 (32.3)	0.46
SSTI	4 (10.0)	3 (9.7)	1.00
IAI	2 (5.0)	1 (3.2)	1.00
UTI	0 (0)	1 (3.2)	0.43
PB	1 (2.5)	0 (0)	1.00
CNS infection	1(2.5)	0 (0)	1.00

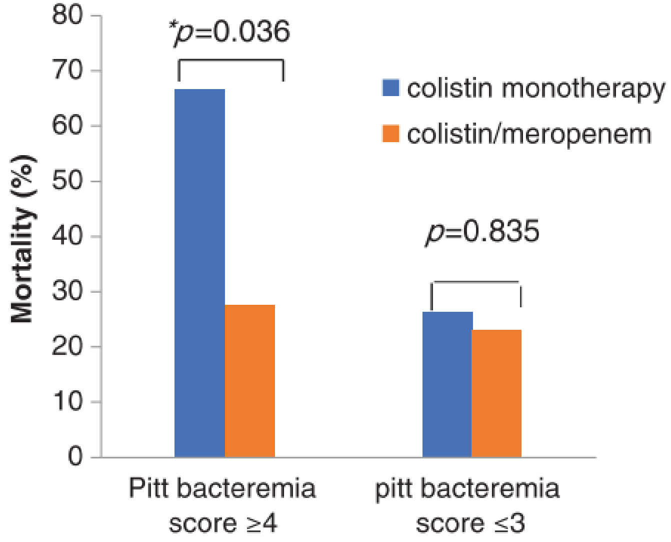


Figure 2. Mortality in the monotherapy and combination therapy groups according to Pitt bacteremia score. *In patients with Pitt bacteremia score ≥4 (n=39), 14-day mortality was significantly higher in patients that received colistin monotherapy (66.7%) compared with those that received colistin plus meropenem (27.8%) (p=0.036).

Table 3. Risk factors for 14-day mortality in patients with CRAB bacteremia in multivariate analysis.

Characteristics	Survivors (n = 44)	Non-survivors (n = 27)	Multivariate analysis	
			OR (95% CI)	*p*
Sex, male	22 (50%)	20 (74.1%)	3.47 (0.79–15.21)	0.098
Age, years	65.34 ± 15.70	69.62 ± 12.77	1.05 (0.99–1.11)	0.095
Lung disease	9 (20.5%)	11 (40.7%)	1.48 (0.33–6.52)	0.604
DM	20 (45.5%)	7 (25.9%)	0.25 (0.05–1.19)	0.082
Cerebrovascular disease	24 (54.5%)	6 (22.2%)	0.37 (0.08–1.76)	0.215
Pitt bacteremia score	3.25 ± 2.22	5.22 ± 2.22	1.63 (1.16–2.30)	0.005
Type of infection-pneumonia	13 (29.5%)	18 (66.7%)	5.27 (1.11–24.87)	0.036
Combination therapy	23 (52.3%)	8 (29.6%)	0.15 (0.03–0.65)	0.011

Park, S. Y., et al. (2019)

Empiric Combination therapy for CRAB

Question 2: What Is the Role of Combination Antibiotic Therapy for the Treatment of Infections Caused by CRAB?

Suggested Approach

Combination therapy with at least 2 active agents, whenever possible, is suggested for the treatment of moderate to severe CRAB infections, at least until clinical improvement is observed, because of the limited clinical data supporting any single antibiotic agent. A single active agent can be considered for the treatment of mild CRAB infections.

Empiric combination therapy (2 or 3 agents) :

High dose ampicillin-sulbactam, minocycline, tigecycline, **colistin,** extended infusion meropenem, novel drug(cefiderocol)

Tamma, P. D., et al. IDSA (2022)

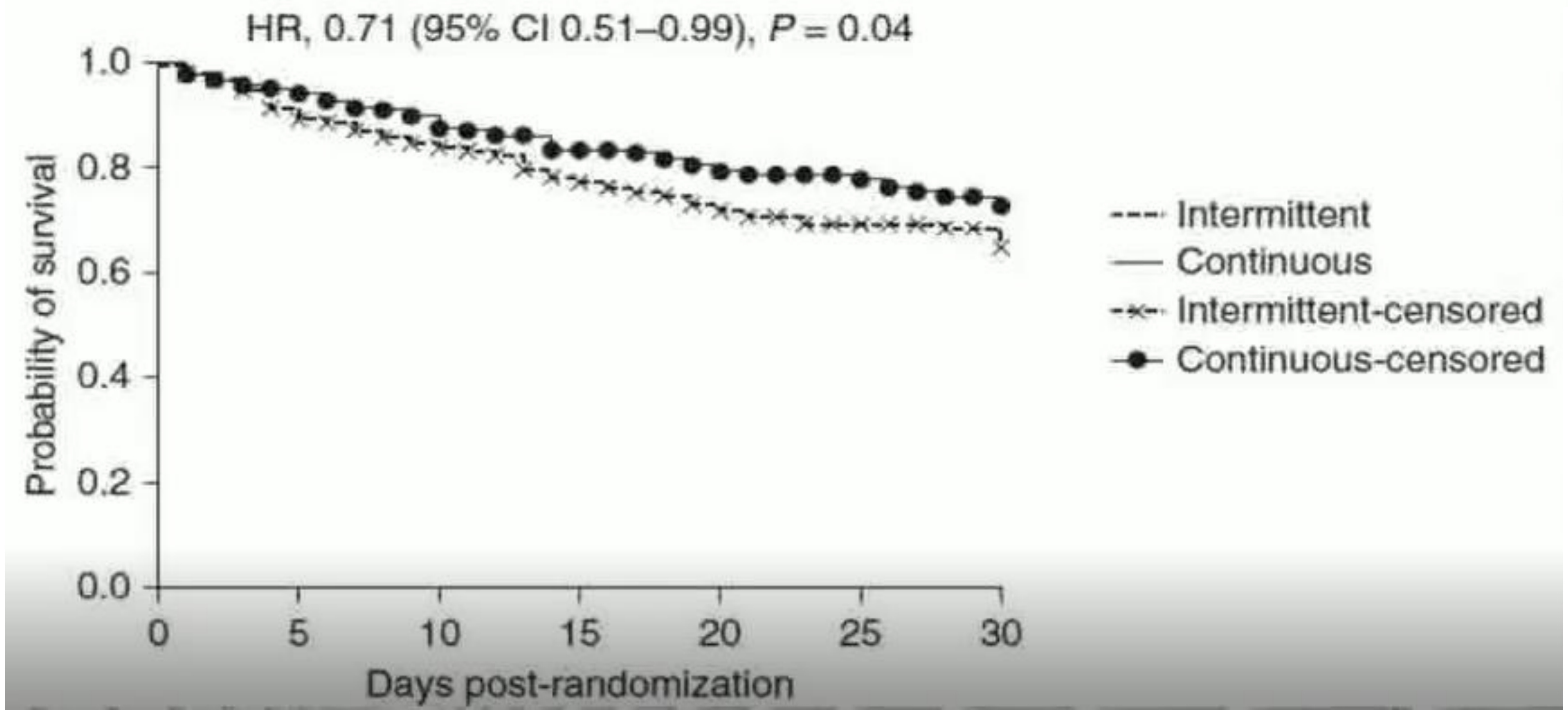
PK/PD – Prolonged infusion of empiric antibiotics targeting MDROs

Beta-lactam antibiotics demonstrate **a time-dependent effect** on bacterial eradication.

A prolonged infusion may therefore improve microbiologic and clinical cure, especially for pathogens with **high MICs.**

→ Continuous infusion (over the entire dosing interval) OR Extended infusion (over three to four hours)

Continuous versus Intermittent β-Lactam Infusion in Severe Sepsis
A Meta-analysis of Individual Patient Data from Randomized Trials



Empiric Combination therapy for MDR P. aeruginosa

Question 1: What are preferred antibiotics for the treatment of infections caused by MDR *P. aeruginosa*?

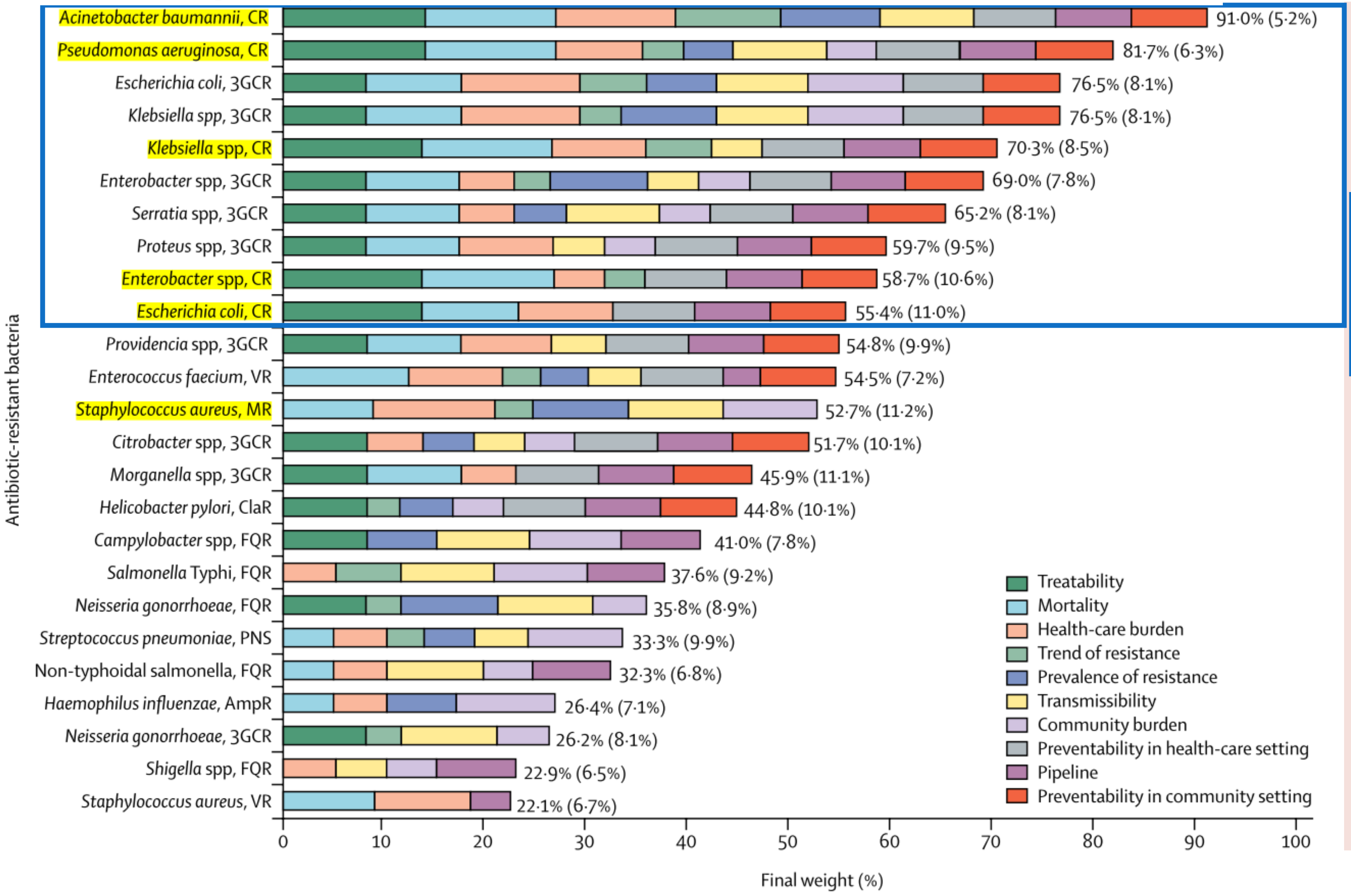
Recommendation: When *P. aeruginosa* isolates test susceptible to traditional non-carbapenem β-lactam agents (i.e., piperacillin-tazobactam, ceftazidime, cefepime, aztreonam), fluoroquinolones (i.e., ciprofloxacin, levofloxacin), they are preferred over carbapenem therapy. For infections caused by *P. aeruginosa* isolates not susceptible to any carbapenem agents but susceptible to traditional β-lactams, the administration of a traditional agent as high-dose extended-infusion therapy is suggested, after antibiotic susceptibility testing results are confirmed. For patients with moderate to severe disease or poor source control with *P. aeruginosa* isolates resistant to carbapenems but susceptible to traditional β-lactams, use of a novel β-lactam agent that tests susceptible (e.g., ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-cilastatin-relebactam) is also a reasonable treatment option.

Carbapenem < **Non-carbapenem beta-lactam** < **High-dose Non-carbapenem extended-infusion** < **Novel beta-lactam**
(carbapenem resistance, CRPA)

Tamma, P. D., et al. IDSA (2022)

Global threats and burdens of MDRO HAP/VAP

Discovery, research, and development of new antibiotics: the WHO priority list of antibiotic-resistant bacteria and tuberculosis



Panel: WHO priority list for research and development of new antibiotics for antibiotic-resistant bacteria

Multidrug-resistant and extensively-resistant *Mycobacterium tuberculosis*[25]

Other priority bacteria

Priority 1: critical

- *Acinetobacter baumannii*, carbapenem resistant
- *Pseudomonas aeruginosa*, carbapenem resistant
- Enterobacteriaceae, carbapenem resistant, third-generation cephalosporin resistant

Priority 2: high

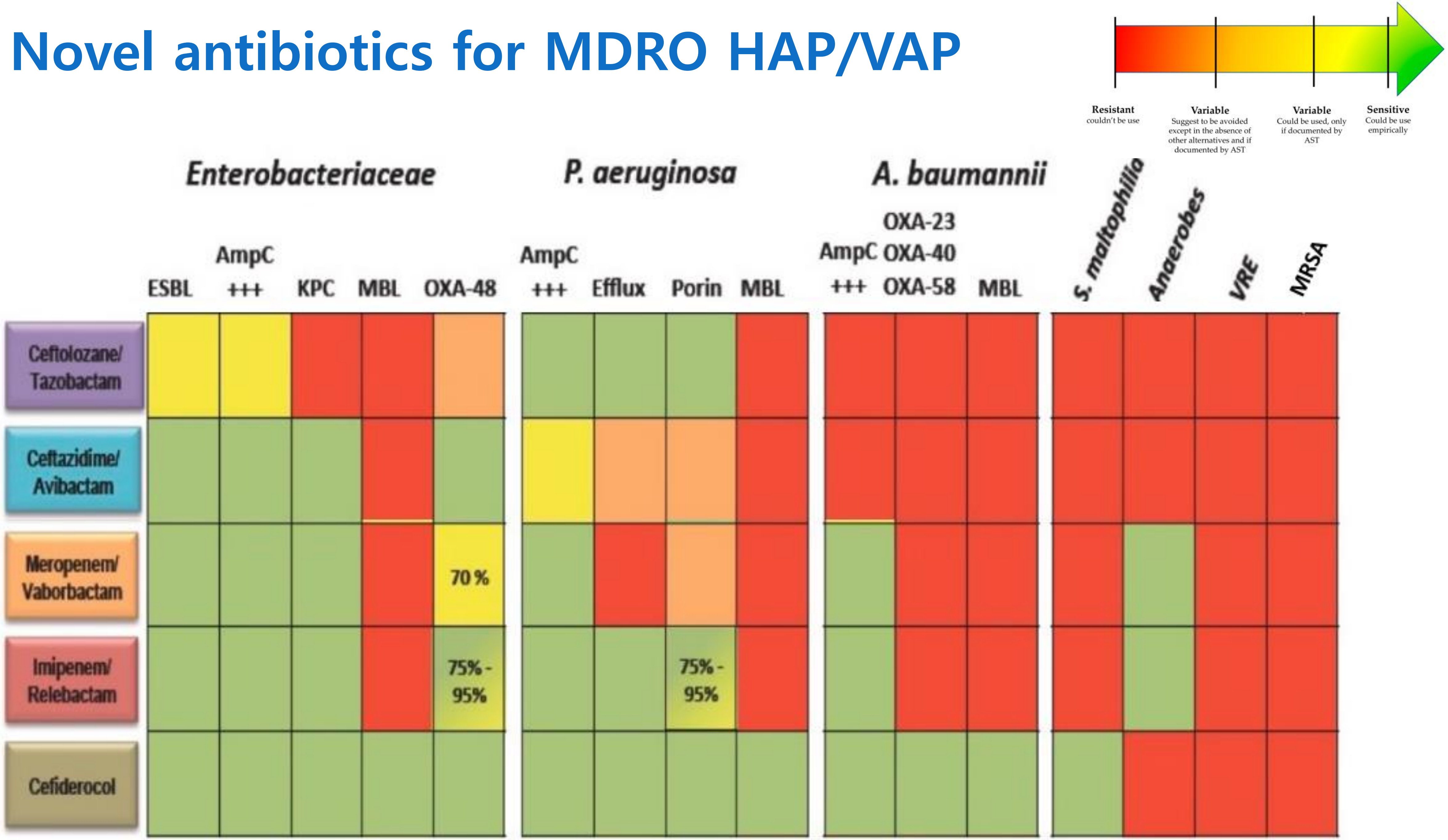
- *Enterococcus faecium*, vancomycin resistant
- *Staphylococcus aureus*, methicillin resistant, vancomycin resistant
- *Helicobacter pylori*, clarithromycin resistant
- *Campylobacter* spp, fluoroquinolone resistant
- *Salmonella* spp fluoroquinolone resistant
- *Neisseria gonorrhoeae*, third-generation cephalosporin resistant, fluoroquinolone resistant

Priority 3: medium

- *Streptococcus pneumoniae*, penicillin non-susceptible
- *Haemophilus influenzae*, ampicillin resistant
- *Shigella* spp, fluoroquinolone resistant

Tacconelli, E., et al. (2018)

Novel antibiotics for MDRO HAP/VAP



Chaïbi, K., et al. (2022)

저박사 주 ZERBAXA INJ [복합제] 식약처 허가(2017.4), 인정비급여(2018.5) 본인 부담

최신 허가사항 변경 안내

- 저박사주_사용상주의사항변경(부작용포함)_20200622
  [식품의약품안전처 | 2020-06-22] 고시문 보기

효능/효과

복잡성 복강내 감염(이 약과 메트로니다졸 병용 투여)
복잡성 요로 감염(신우신염 포함)
원내 감염 폐렴(인공호흡기 관련 폐렴 포함)

용법/용량

CrCL > 50 mL/min 인 18세 이상, 1시간 이상 정주
복잡성 복강내 감염: 본제 1.5g (세프톨로잔 1 g/타조박탐 0.5 g), 8시간마다, 4-14일간
복잡성 요로감염: 본제 1.5g, 8시간마다, 7일간
원내 감염 폐렴: 본제 3g, 8시간마다, 8-14일간.

MSD 항생제 '저박사주' 급여권 진입, 약평위 통과

박양명 기자 | 발행날짜: 2022-06-02 16:07:30

MedicalTimes 19th

심평원, 약평위 결과 공개…급여 적정성 인정
비용효과성 불분명으로 비급여 판정 받은지 3년만

한국MSD 항생제 저박사주

[메디칼타임즈=박양명 기자] 한국MSD 항생제 '저박사주'가 급여권 진입에 성공했다. 비용효과성이 불분명하다는 이유로 비급여 판정을 받은지 3년만이다.

건강보험심사평가원은 이같은 내용을 담은 제6차 약제급여평가위원회(이하 약평위) 심의 결과를 2일 공개했다.

약평위는 다제내성균 항생제 저박사주(세프톨로잔/타조박탐)는 '복잡성 복강내 감염 및 복잡성 요로감염, 원내 감염 폐렴'에 대해 급여 적정성이 있다는 판단을 내렸다. 약평위를 통과한 저박사주는 건강보험공단과 약가협상을 가질 예정이다.

저박사는 세파로스포린 항생제인 세프톨로잔에 베타-락타마제 억제제인 타조박탐을 더한 복합 항생제로 2014년 미국 식품의약국(FDA)의 승인을 받은 약물이다. 3년 전만해도 약평위는 제약사 측의 급여 신청가가 고가라며 비용효과성이 불분명하다며 비급여 결정을 내린 바 있다.

MSD '저박사', 그람음성균 새 치료대안으로 조명

마테오 바세티 이탈리아감염학회 부회장 '그람음성균 최신 치료지견' 발표

의료계 정론 메디포뉴스
medifonews

▲ 마테오 바세티 이탈리아감염학회 부회장

바세티 교수는 녹농균, ESBL 생성 그람음성균 내성률 감소를 위한 카바페넴 대체 필요성을 강조했다. 그는 "ESBL생성 그람음성균 증가로 치료제인 카바페넴 사용이 계속 늘고 있으며, 이로 인해 카바페넴 내성균주가 출현하고 있다"며 "사용 가능한 치료 옵션을 보유하여 현재로서 ESBL생성 그람음성균에 대한 치료의 보루로 여겨지는 카바페넴을 반드시 필요할 때 사용할 수 있도록 해야 한다"고 강조했다.

또한, 최신 연구결과들을 인용해 신규 항생제 및 개발 중인 항생제가 카바페넴을 대체하는 데 효과적일 수 있다고 설명했다.

이 세션에서 항생제 내성 그람음성균 치료의 새 대안으로써 '저박사'의 유용성도 제시되었다. '저박사'는 ESBL 생성 장내세균, 다제내성 녹농균 등 그람음성균에 대한 광범위한 효능을 입증했으며, 카바페넴계 항생제인 메로페넴과 유사한 수준의 임상적 완치율을 확인했다.

복잡성 복강내 감염 환자를 대상으로 한 임상에서(mITT 군 대상) 저박사(메트로니다졸 병용)의 치료율은 83.0%, 메로페넴의 치료율은 87.3%로 유사한 효능을 입증했다. '저박사'는 특히 녹농균 치료에 있어 메로페넴(79.1%)보다 더 높은 91.7%의 감수성을 보여 카바페넴의 대체 가능성을 보였다.

바세티 교수는 "녹농균은 내성이 매우 발현되기 쉬우며, 현재 녹농균에 대한 경험적 병용요법의 백본으로 카바페넴계 항생제 및 세프타지딤을 사용하지만, 향후 저박사가 이를 대체할 것으로 본다"고 말했다.

Empiric Combination therapy for DTP (Difficult to Treat P.aeruginosa)

Non-susceptibility to all of the following:
piperacillin-tazobactam, ceftazidime, cefepime, aztreonam, meropenem, imipenem-cilastatin, ciprofloxacin, and levofloxacin.

Question 4: What are preferred antibiotics for the treatment of infections outside of the urinary tract caused by DTR-*P. aeruginosa*?

Recommendation: Ceftolozane-tazobactam, ceftazidime-avibactam, and imipenem-cilastatin-relebactam, as monotherapy, are preferred options for the treatment of infections outside of the urinary tract caused by DTR-*P. aeruginosa*.

Cefiderocol is recommended as an alternative treatment option.

Question 6: What is the role of combination antibiotic therapy for the treatment of infections caused by DTR-*P. aeruginosa*?

Recommendation: Combination antibiotic therapy is not routinely recommended for infections caused by DTR-*P. aeruginosa* if *in vitro* susceptibility to a first-line antibiotic (i.e., ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam) has been confirmed.

Empiric Novel beta-lactam + Aminoglycosides combination → Definitive continued monotherapy

Tamma, P. D., et al. IDSA (2022)

Empiric algorithm for HAP/VAP in ICU (The Far Future in Korea?)

Suspected nosocomial pneumonia in the ICU

Early onset without previous AT

VAP

Zaragoza, R., et al. (2020)

Colistin (후콜리스티메테이트주)

허가정보 · 복약정보

전 체	효능 · 효과	용법 · 용량	주의사항

■ 효능 · 효과

유효균종 : 엔테로박터 에로제니즈, 폐렴간균, 다른 항생물질에 내성인 대장균, 녹농균
적응증 : 주효능효과 방광염, 신우신염

고시제목	Colistimethate 주사제 (후콜리스티메테이트주 등)		
고시번호	제2017-193호(약제)	시행일	2017-11-01

■ 세부인정기준

1. 허가사항 범위 내에서 아래와 같은 기준으로 투여 시 요양급여를 인정하며, 동 인정기준 이외에는 약값 전액을 환자가 부담토록 함.

- 아 래 -

○ 1차 약제(Quinolone계 항생제 등) 투여로 증상이 호전되지 않는 방광염, 신우신염 환자에게 투여 시 인정함.

2. 허가사항 범위(효능 · 효과)를 초과하여 아래와 같은 기준으로 투여 시 요양급여를 인정함.

- 아 래 -

가. 기존 모든 항생제에 내성을 보이는 아시네토박터 바우마니균(Acinetobacter baumanii)
나. 기존 모든 항생제에 내성을 보이는 녹농균 (Pseudomonas aeruginosa)

Linezolid (자이복스주)

[허가사항]
병원내감염 폐렴
지역감염 폐렴(세균혈증을 동반한 경우 포함)
합병증을 동반한 피부 및 연조직 감염(당뇨병성 족부감염 환자 포함, 골수염 동반되지 않은 경우)
합병증을 동반하지 않은 피부 및 연조직 감염
반코마이신-내성 엔테로코쿠스 페시움 감염(세균혈증을 동반한 경우 포함)

[보험인정기준]
1.허가사항 범위 내 아래와 같은 기준으로 투여 시 요양급여를 인정하며, 동 인정기준 이외에는 약값 전액을 환자 부담

- 아 래 -

가. 혈액배양검사(Blood culture) 또는 무균적체액(CSF, Ascites, Pleural effusion 등)에서 반코마이신저항성 엔테로코커스 패슘(Enterococcus faecium)이 증명된 경우에 인정

나. 메티실린내성황색포도상구균(MRSA)에 투여 시에는 Vancomycin이나 Teicoplanin 투여 시 임상적 및 이학적 검사상 반응이 없는 것이 확인된 경우에 인정하고 두 약제에 알러지가 있는 경우에 투여 시에도 인정

2. 허가사항 범위를 초과하여 아래와 같은 기준으로 투여 시 요양급여를 인정함.

- 아 래 -

○ 투여기준
리팜핀 내성/다제내성 결핵 환자에게 2019년 WHO 지침의 권고내역 및 약제구성원칙에 따라 투여하는 경우

[보건복지고시 제2020-265호(약제), 시행일지 2020.12.01]

Rapid diagnosis of bacteria and resistance mechanisms

Potential Impact of Rapid Multiplex PCR on Antimicrobial Therapy Guidance for Ventilated Hospital-Acquired Pneumonia in Critically Ill Patients, A Prospective Observational Clinical and Economic Study

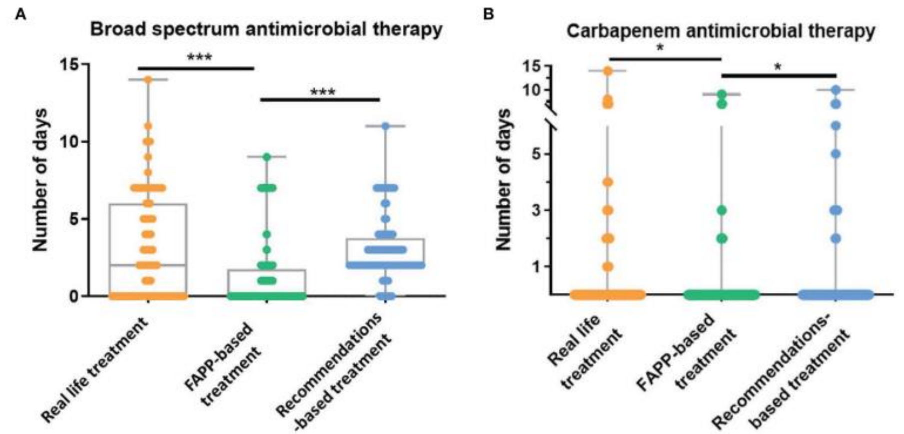


FIGURE 1 | Duration of broad-spectrum antimicrobial therapy. (A, B). Numbers of days of (A) broad-spectrum antimicrobial therapy (activity against P. aeruginosa), and (B) carbapenems with anti-pseudomonas aeruginosa activity in real-life, in the FAPP-based simulated treatment, and the recommendations-based simulated treatment. FAPP, FilmArray® Pneumonia plus Panel. *p < 0.01, ***p < 0.001.

Antimicrobial therapy guidance by Rapid Multiplex PCR

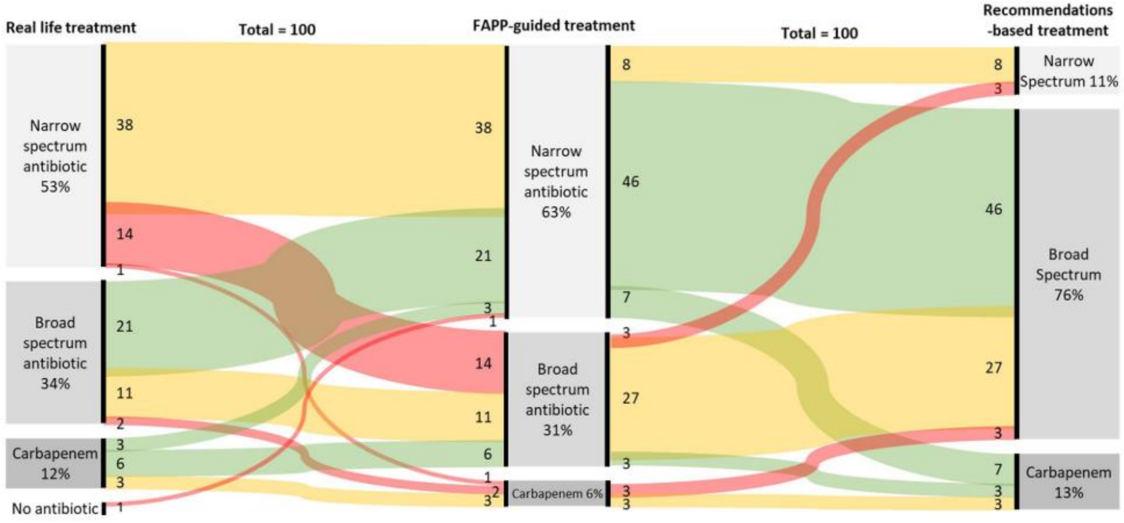


FIGURE 2 | Sankey chart of real-life empirical treatments implemented without FAPP (left column), antimicrobial therapies simulated with the results of FAPP (Middle column), and antimicrobial therapies simulated by following the actual recommendations (right column). Red lines stand for antibiotic escalation, green for de-escalation, and yellow for no changes.

Conclusions: Our results suggest that using FAPP in patients with VHAP has the potential to reduce the use of broad-spectrum antimicrobial therapy without increasing the risk of microbial treatment failure.

Rapid diagnosis of bacteria and resistance mechanisms

Molecular method	ID/AST	Examples	Pathogen/Resistance detection		Turnaround time	Clinical considerations
Real-time PCR	±	GeneXpert MRSA/SA	MRSA, MSSA, mec A/C		≤2 h	Prompt differentiation between MRSA and MSSA
	±	BD MAX MRSA XT	MRSA, MSSA, mec A/C		≤2 h	
	±	GeneXpert Carba-R	KPC, NDM, VIM, OXA-48, IMP		≤2 h	Prompt identification of carbapenem resistance genes
Multiplex PCR	±	BioFire Film Array	Viruses: Adenovirus Coronavirus Human metapneumovirus Human rhinovirus Huma enterovirus Influenza A/B Parainfluenza virus Respiratory syncytial virus Antimicrobial Resistance Genes: Methicillin resistance- mec A/C and MREJ Carbapenemases- KPC NDM OXA-48-like VIM IMP ESBL- CTX-M	Bacteria: A. calcoaceticus–baumannii complex E. cloacae complex E. Coli H. influenzae K. aerogenes K. oxytoca K. pneumoniae group M. catarrhalis Proteus spp. P. aeruginosa S. marcescens S. aureus S. agalactiae S. pneumoniae S. pyogenes Atypical bacteria: C. pneumoniae L. pneumophila M. pneumoniae	≤2 h	• Comprehensive number of targets. • Rapid turnaround. • Identify presence of bacterial resistance genes. • Semi-quantitative bacterial analysis. • BAL (SENS 96%; SPEC98%).a • Sputum (SENS 96%; SPEC 97%).a
	±	Curetis Unyvero LRT Panel	Fungi: P. jirovecii Antimicrobial Resistance Genes: Carbapenemases- OXA-48 OXA-58 VIM IMP KPC NDM OXA-23 OXA-24/40 ESBL- CTX-M Methicillin resistance- mec A/C Penicillin: TEM SHV	Bacteria: Acinetobacter spp. C. pneumoniae C. freundii E. cloacae complex E. coli H. influenzae K. aerogenes K. oxytoca K. pneumoniae K. variicola L. pneumophila M. catarrhalis M. morganii M. pneumoniae Proteus spp. P. aeruginosa S. marcescens S. aureus S. maltophilia S. pneumoniae	4–5 h	• Comprehensive number of targets. • Rapid turnaround. • Identify presence of bacterial resistance genes. • Semi-quantitative bacterial analysis.

Renaud, C. and M. H. Kollef (2022).

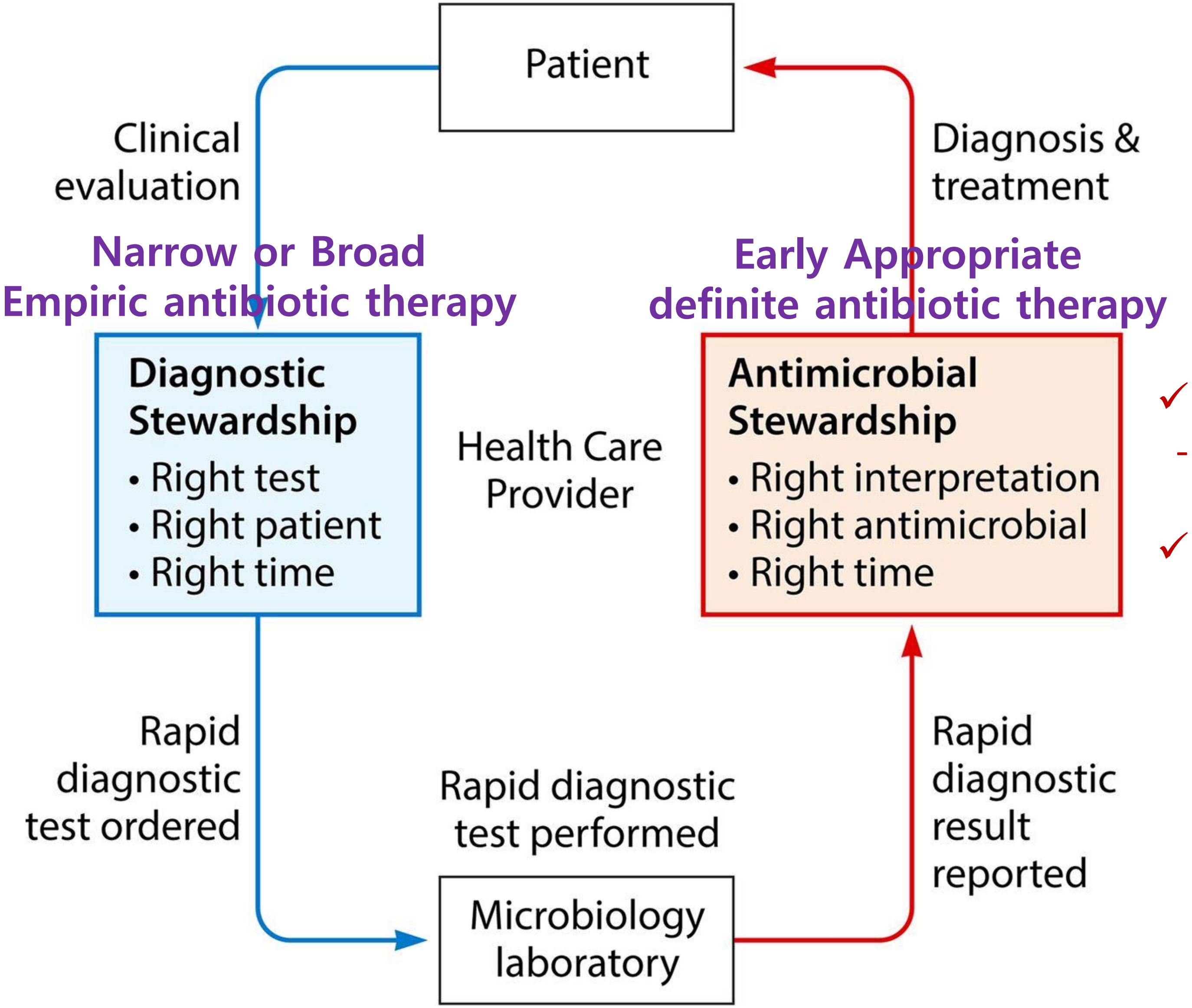
Rapid diagnosis of bacteria and resistance mechanisms

Table 2. Advantages and disadvantages of multiplex PCR panels.

Advantages	Disadvantages
Exceptionally faster time to results for pathogen and resistance profiles: major utility for prompt treatment modification and effective patient management	Over-detection of microbial and viral genome: problem in results interpretation: pathogen or coloniser? (may be partially solved with semi-quantification of bacterial targets)
Multiple targets detection at the same and Detection of viral and atypical pathogens as well	The presence of a resistance gene marker may not be linked to the detected microorganism, but to other co-existent organisms either undetectable or below the detection limit, thus making culture-based techniques still necessary in many cases
Detection of pathogens even when antimicrobial treatment has been initiated	Initial cost to buy the equipment
Potential for better antibiotic utilisation and positive impact on: -nosocomial pneumonia management, shortening hospital stay and decreasing healthcare costs, -antibiotic stewardship programs	Not widely available among different institutions yet

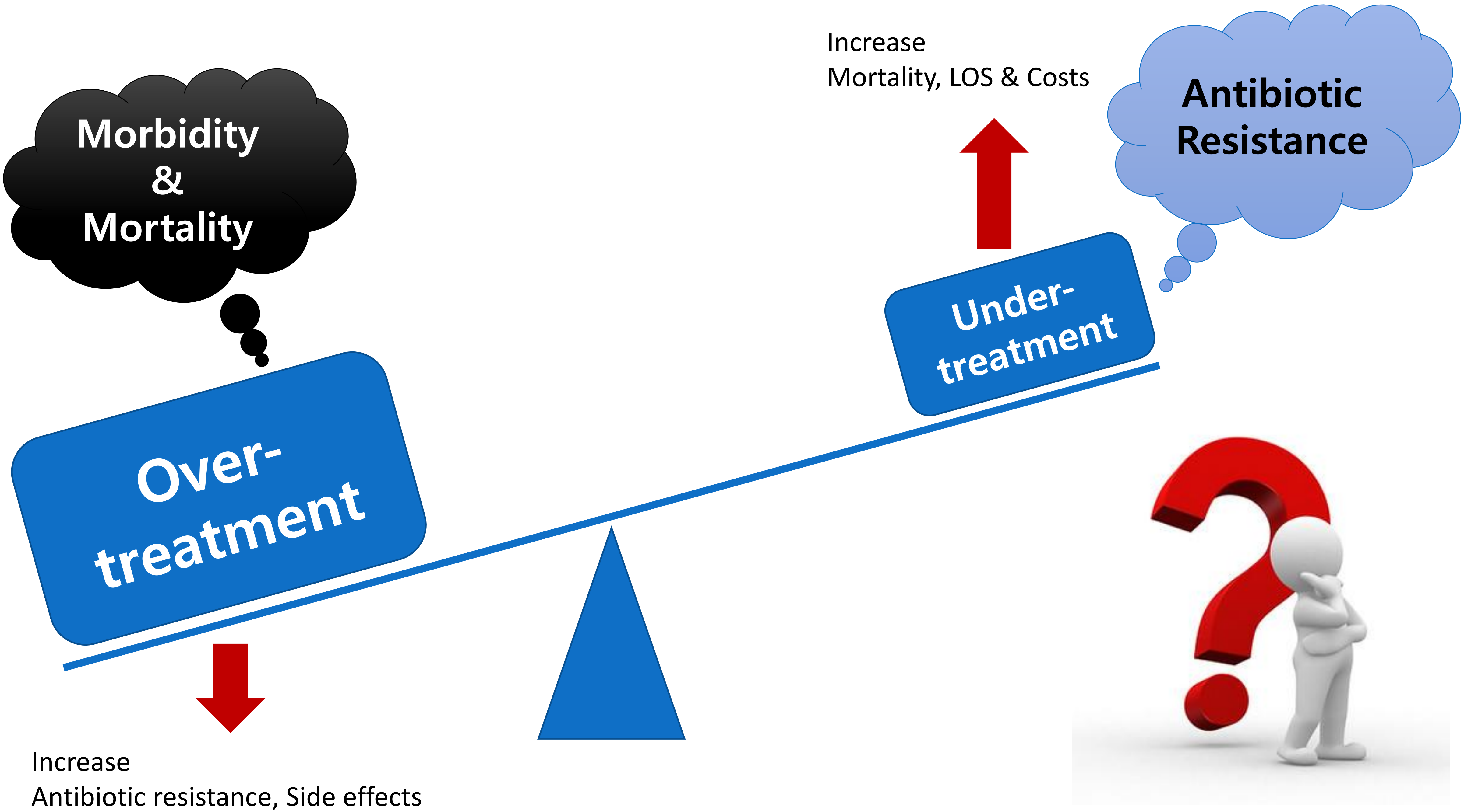
Implementation of Rapid Molecular Infectious Disease Diagnostics : the Role of Diagnostic and Antimicrobial Stewardship

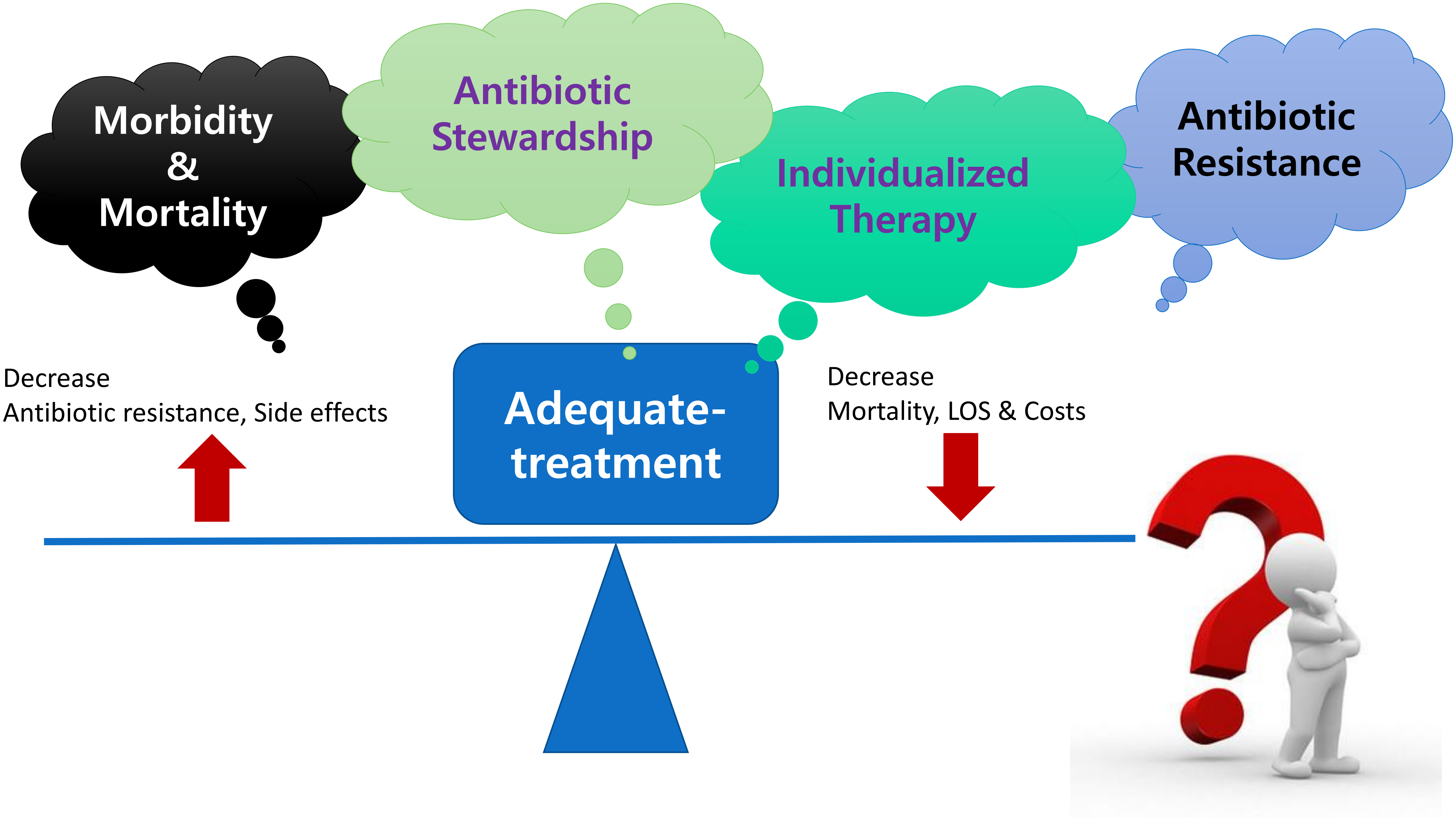
- ✓ Sensitivity & Specificity
- ✓ Predictive values
- ✓ Laboratory feasibility
- ✓ Cost
- ✓ Clinical impact
- ✓ On-demand or Batched
- ✓ Run time
- ✓ Result reporting time



- ✓ Clinical practice guidelines
  - Modifying antimicrobials based on the test result
- ✓ Real-time decision support

Messacar, K., et al. (2017)


Morbidity
&
Mortality
Over-
treatment
Increase
Antibiotic resistance, Side effects
Increase
Mortality, LOS & Costs
Antibiotic
Resistance
Under-
treatment


Morbidity & Mortality
Antibiotic Stewardship
Individualized Therapy
Antibiotic Resistance
Decrease
Antibiotic resistance, Side effects
Adequate-treatment
Decrease
Mortality, LOS & Costs

Summary (Initial Empiric antibiotics for HAP/VAP)

- Recent epidemiologic studies showed increasing MDR GNB pathogen and decreasing MRSA in Korea.
- According to epidemiology, etiologic organism is not different between HAP and VAP.
- MDR increases IET (Inappropriate empiric therapy) and bad outcomes.
- Concerns on the future antibiotic resistance and drug toxicity should be considered.
- Routine anti-pseudomonal combination therapy (beta-lactam + FQ) didn't show survival benefit in our study.
- Empirical combination therapy is indicated according to local ecology or surveillance cultures for the patients with very high risk of mortality.
- Development and Distribution of Newer antibiotics for MDRO are needed.
- If molecular diagnostics is used in practice, empiric therapy might be more accurate & rapid.
- Antimicrobial stewardship should be implemented to the daily practice of pulmonologists and intensivists to reduce the future resistance and improve patient's outcome.

Ideal Empiric therapy in HAP/VAP?

-경청해주셔서 감사합니다-

Clinical Practice Guideline

Host
MDR risk factors

Mortality risk

Epidemiology
-National
-Per Hospital
-Per Unit

Colonization

Newer antibiotics

Rapid molecular diagnostics

Antibiotic stewardship