Pseudomonas 환자의 치료

고려대학교 구로병원 호흡기내과 오지연

- Key Question

For patients with pseudomonas infection after confirming the culture result, should be considered for combination antibiotics?

- Proportion & resistance of Pseudomonas in HAP/VAP

- Role of combination therapy versus monotherapy in definitive therapy for pseudomonas
  - HAP/VAP
  - Bacteremia
  - MDR

Proportion & resistance of pseudomonas in HAP/VAP

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

Doo Ryeon Chung[1,2], Jae-Hoon Song[1,2], So Hyun Kim[2], Visanu Thamlikitkul[3], Shao-Guang Huang[4], Hui Wang[5]*, Thomas Man-kit So[6], Rohani M. D. Yasin[7], Po-Ren Hsueh[8], Celia C. Carlos[9], Li Yang Hsu[10], Latre Buntaran[11], M. K. Lalitha[12], Min Ja Kim[13], Jun Yong Choi[14], Sang Il Kim[15], Kwan Soo Ko[2,16], Cheol-In Kang[1], and Kyong Ran Peck[1] on behalf of the Asian Network for Surveillance of Resistant Pathogens Study Group‡

[1]Division of Infectious Diseases, Samsung Medical Center, and [16]Department of Molecular Cell Biology, Sungkyunkwan University School of Medicine, Seoul, Korea; [2]Asia Pacific Foundation for Infectious Diseases, Seoul, Korea; [3]Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; [4]Department of Respiratory Medicine, Rui Jin Hospital, Shanghai, China; [5]Department of Clinical Laboratories, Peking Union Medical College Hospital, Beijing, China; [6]Department of Medicine, Princess Margaret Hospital, Hong Kong; [7]Bacteriology Unit, Specialized Diagnostic Centre, Institute for Medical Research, Kuala Lumpur, Malaysia; [8]Department of Laboratory Medicine, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan; [9]Antimicrobial Resistance Surveillance Reference Laboratory, Research Institute for Tropical Medicine, Manila, Philippines; [10]Department of Medicine, National University Hospital, Singapore; [11]Children's and Maternity, Harapan Kita Hospital, Jakarta, Indonesia; [12]Department of Microbiology, Madras Medical Mission, Chennai, India; [13]Division of Infectious Diseases, Korea University College of Medicine, Seoul, Korea; [14]Division of Infectious Diseases, Yonsei University College of Medicine, Seoul, Korea; and [15]Division of Infectious Diseases, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea

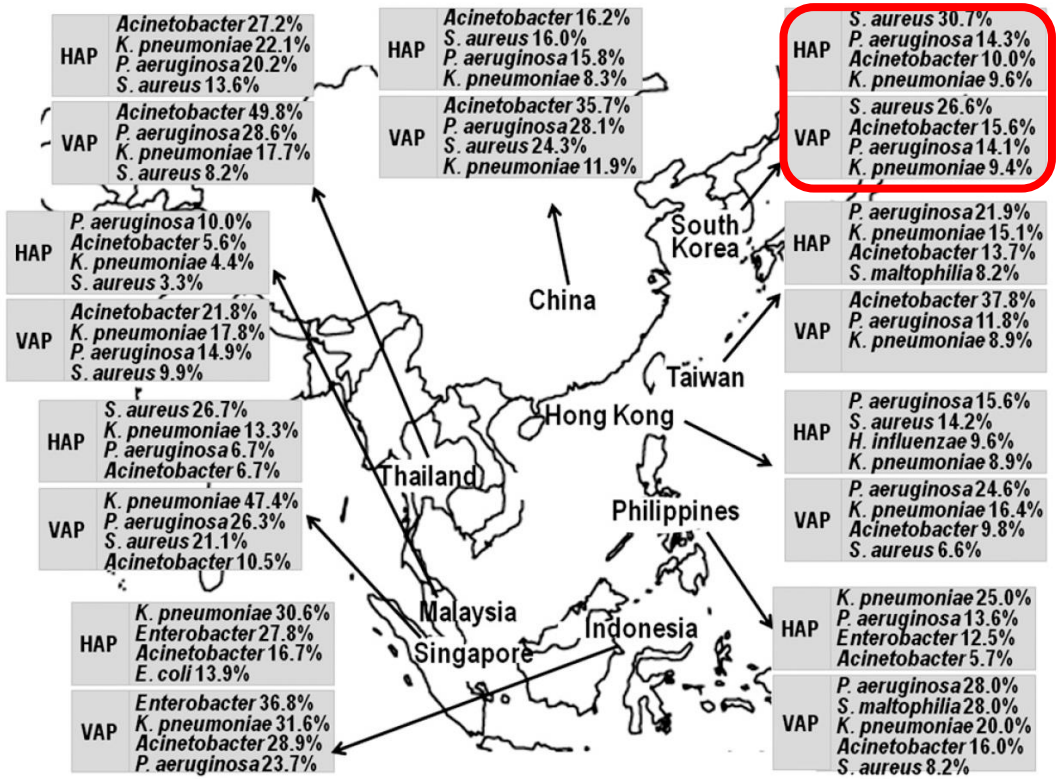

Figure 1. Comparison of major microorganisms isolated from hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) in Asian countries.

A prospective surveillance study
73 hospitals in 10 Asian countries from 2008–2009.
A total of 2,554 cases with HAP or VAP in adults were enrolled and 2,445 bacterial isolates were collected from 1,897 cases

Am J Respir Crit Care Med Vol 184. pp 1409–1417, 2011

ORIGINAL ARTICLE | ISSN: 1738-3536(Print)/2005-6184(Online) • Tuberc Respir Dis 2021;84:317-325

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

Ryoung-Eun Ko, M.D., Ph.D.[1,*], Kyung Hoon Min, M.D., Ph.D.[2,*], Sang-Bum Hong, M.D., Ph.D.[3], Ae-Rin Baek, M.D., Ph.D.[4], Hyun-Kyung Lee, M.D., Ph.D.[5], Woo Hyun Cho, M.D., Ph.D.[6], Changhwan Kim, M.D., Ph.D.[7], Youjin Chang, M.D., Ph.D.[8], Sung-Soon Lee, M.D., Ph.D.[9], Jee Youn Oh, M.D., Ph.D.[2], Heung Bum Lee, M.D., Ph.D.[10], Soohyun Bae, M.D., Ph.D.[11,†], Jae Young Moon, M.D., Ph.D.[12,†], Kwang Ha Yoo, M.D., Ph.D.[13], Kyeongman Jeon, M.D., Ph.D.[1,14], on behalf of the Korean HAP/VAP Study Group
Author affiliations appear at the end of this article.

- 전체 17%
- Gram (-) 중 21.6%

from June 1 to December 31, 2019 13 hospitals

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
MDR pathogen identified‡, n (%)	138 (70.4)
Acinetobacter species	67
Pseudomonas aeruginosa	30
Enterobacteriaceae	27
Staphylococcus aureus	19
Enterococcus species	4

*Others included one *Streptococcus pyogenes*, one *Streptococcus mitis*, one *Streptococcus agalactiae*, one *Streptococcus angiosus*, and one *Listeria monocytogenes*. †Others included one *Klebsiella oxytoca* and one *Raoultella planticola*. ‡Data were available for 196 patients.
MDR: multidrug resistance.

국내

Tuberc Respir Dis 2021;84:317-325

Journal of Global Antimicrobial Resistance 29 (2022) 527–533

Contents lists available at ScienceDirect

Journal of Global Antimicrobial Resistance

journal homepage: www.elsevier.com/locate/jgar

In vitro activity of ceftolozane/tazobactam against Gram-negative isolates collected from ICU patients with lower respiratory tract infections in seven Asian countries—SMART 2017–2019

Sibylle H. Lob[a,*], Krystyna M. Kazmierczak[a], Wei-Ting Chen[b], Fakhar Siddiqui[c], C. Andrew DeRyke[c], Katherine Young[c], Mary R. Motyl[c], Daniel F. Sahm[a]

[a] IHMA, Schaumburg, IL 60173, USA
[b] MSD, Taipei, Taiwan
[c] Merck & Co., Inc., K

Table 1
Species distribution of Gram-negative isolates collected from ICU patients with lower respiratory tract infections.

Species	*n* (%), rank order							
	All	Hong Kong	South Korea	Malaysia	Philippines	Taiwan	Thailand	Vietnam
Klebsiella pneumoniae	898 (27.3), 1	14 (15.6), 2	97 (20.9), 3	141 (36.8), 1	47 (27.5), 1	201 (22.0), 2	182 (31.5), 1	216 (31.4), 2
Acinetobacter baumannii complex[a]	780 (23.7), 2	3 (3.3), 7	157 (33.8), 1	85 (22.2), 3	18 (10.5), 3	141 (15.4), 3	135 (23.4), 2	241 (35.0), 1
Pseudomonas aeruginosa	761 (23.1), 3	24 (26.7), 1	102 (22.0), 2	96 (25.1), 2	41 (24.0), 2	267 (29.2), 1	126 (21.8), 3	105 (15.3), 3
Stenotrophomonas maltophilia	181 (5.5), 4	14 (15.6), 2	25 (5.4), 4	10 (2.6), 5	18 (10.5), 3	78 (8.5), 4	34 (5.9), 4	2 (0.3), 10
Escherichia coli	172 (5.2), 5	11 (12.2), 4	16 (3.4), 6	10 (2.6), 5	13 (7.6), 5	60 (6.6), 5	24 (4.2), 5	38 (5.5), 4
Klebsiella aerogenes	78 (2.4), 6	5 (5.6), 6	25 (5.4), 4	7 (1.8), 7	5 (2.9), 7	14 (1.5), 9	8 (1.4), 8	14 (2.0), 6
Serratia marcescens	75 (2.3), 7	7 (7.8), 5	12 (2.6), 7	3 (0.8), 9	0	30 (3.3), 7	13 (2.2), 6	10 (1.5), 7
Acinetobacter nosocomialis	67 (2.0), 8	2 (2.2), 8	4 (0.9), 9	6 (1.6), 8	1 (0.6), 8	31 (3.4), 6	6 (1.0), 9	17 (2.5), 5
Enterobacter cloacae	66 (2.0), 9	2 (2.2), 8	5 (1.1), 8	13 (3.4), 4	7 (4.1), 6	23 (2.5), 8	13 (2.2), 6	3 (0.4), 9
Proteus mirabilis	21 (0.6), 10	0	2 (0.4), 10	2 (0.5), 10	0	9 (1.0), 10	4 (0.7), 10	4 (0.6), 8
Other species	189 (5.7)	8 (8.9)	19 (4.1)	10 (2.6)	21 (12.3)	60 (6.6)	33 (5.7)	38 (5.5)
Total	3288 (100)	90 (100)	464 (100)	383 (100)	171 (100)	914 (100)	578 (100)	688 (100)

[a] Defined as isolates of *A. baumannii* and isolates assigned to the complex based on the matrix-assisted laser desorption/ionisation-time of flight (MALDI-TOF) score.

In 2017–2019, up to 100 consecutive, aerobic Gram-negative LRTI isolates were collected per year at each of 37 hospitals

Journal of Global Antimicrobial Resistance 29 (2022) 527–533

Original Article

Different microbiological and clinical aspects of lower respiratory tract infections between China and European/American countries

Xin Zhang[1], Rui Wang[2], Xiuzhen Di[2], Bin Liu[1], Youning Liu[1]

[1]Department of Respiratory Diseases, [2]Department of Clinical Pharmacology, Chinese PLA General Hospital, Beijing 100853, China
Corresponding to: Youning Liu, MD. Department of Respiratory Diseases, Chinese PLA General Hospital, Beijing 100853, China. Email: liuyn301@126.com.

Journal of Thoracic Disease, Vol 6, No 2 February 2014

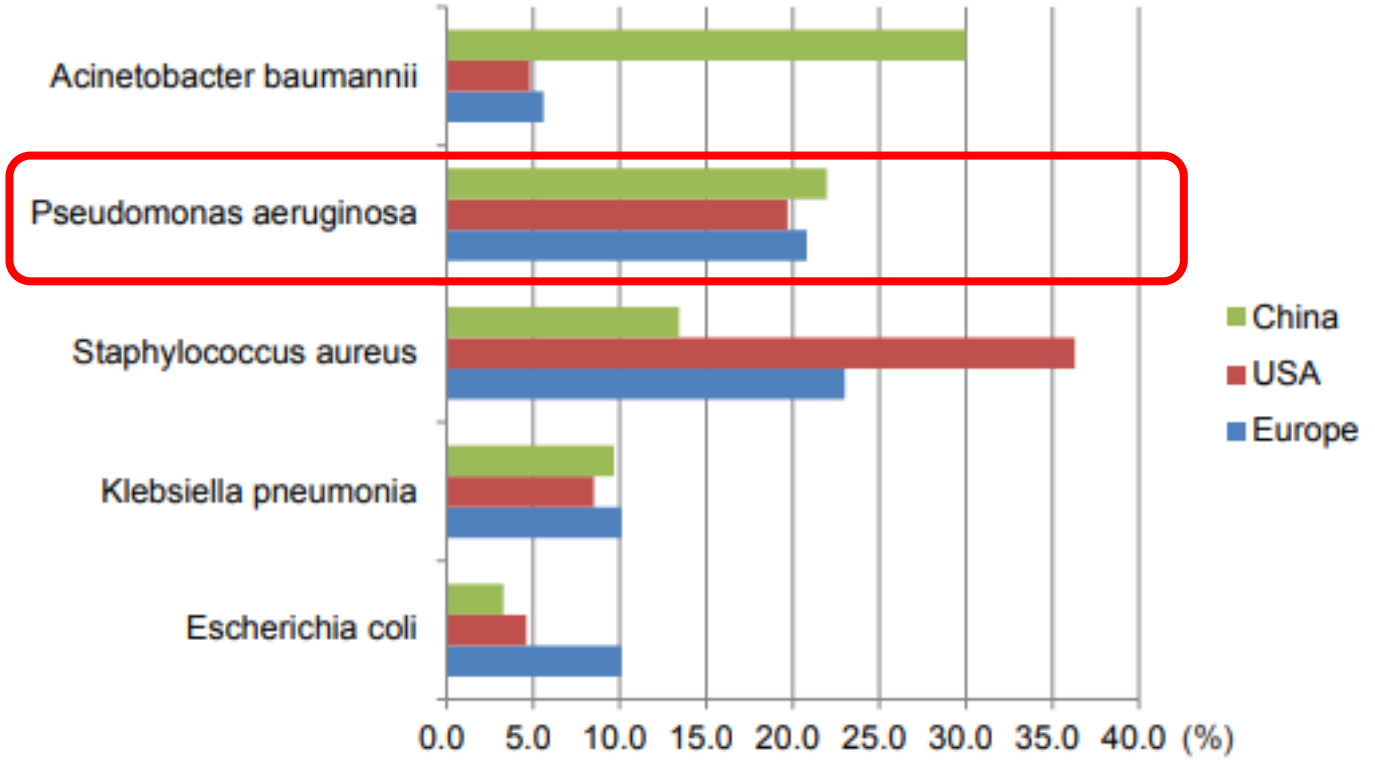

Figure 2 Regional incidence (%) of pathogens isolated from patients with hospital-acquired pneumonia (HAP).

J Thorac Dis 2014;6(2):134-142

J Korean Med Sci. 2021 Nov 8;36(43):e273
https://doi.org/10.3346/jkms.2021.36.e273
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Infectious Diseases, Microbiology & Parasitology

Check for updates

Antimicrobial Susceptibility Trends and Risk Factors for Antimicrobial Resistance in *Pseudomonas aeruginosa* Bacteremia: 12-Year Experience in a Tertiary Hospital in Korea

OPEN ACCESS

Received: Jun 19, 2021
Accepted: Sep 12, 2021

Address for Correspondence:
Chisook Moon, MD, PhD
Division of Infectious Diseases, Department of Internal Medicine, Inje University Busan Paik

Jin Suk Kang,[1] **Chisook Moon**,[1] **Seok Jun Mun**,[1] **Jeong Eun Lee**,[2] **Soon Ok Lee**,[2] **Shinwon Lee**,[2] **and Sun Hee Lee** [2]

[1]Division of Infectious Diseases, Department of Internal Medicine, Inje University Busan Paik Hospital, Inje University College of Medicine, Busan, Korea
[2]Division of Infectious Diseases, Department of Internal Medicine, Pusan National University School of Medicine and Medical Research Institute, Pusan National University Hospital, Busan, Korea

retrospectively reviewed the medical records of patients with P. aeruginosa bacteremia admitted to Inje University Busan Paik Hospital, Busan, South Korea, from January 2009 to October 2020

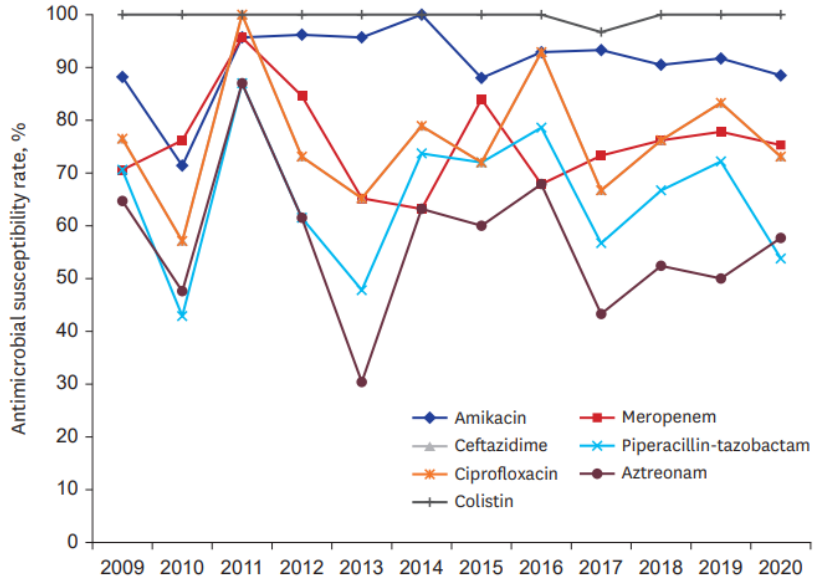

Fig. 1. Annual antimicrobial susceptibility trends in *P. aeruginosa* bacteremia.

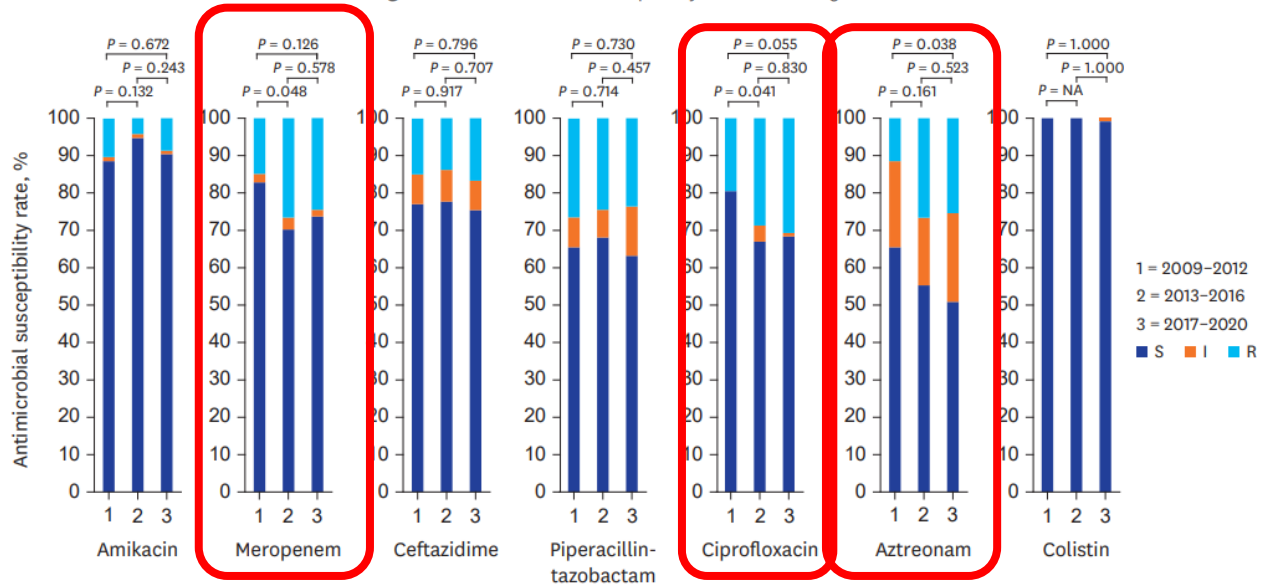

Fig. 2. Results of antimicrobial susceptibility in *P. aeruginosa* bacteremia for 2009–2012, 2013–2016, and 2017–2020. The *P* value was a comparison between susceptible and non-susceptible.
NA = not applicable, S = susceptible, I = intermediate, R = resistant.

국내 J Korean Med Sci. 2021 Nov 8;36(43):e273

Table 1. Antimicrobial susceptibility rates in *P. aeruginosa* bacteremia

Characteristics	Total (n = 295)	2009–2012 (n = 87)	2013–2016 (n = 94)	2017–2020 (n = 114)	*P*
Amikacin	269 (91.2)	77 (88.5)	89 (94.7)	103 (90.4)	0.316
Gentamicin	246 (83.4)	75 (86.2)	82 (87.2)	89 (78.1)	0.147
Imipenem	220 (74.6)	71 (81.6)	65 (69.1)	84 (73.7)	0.151
Meropenem	222 (75.3)	72 (82.8)	66 (70.2)	84 (73.7)	0.131
Cefepime	228 (77.3)	68 (78.2)	76 (80.9)	85 (74.6)	0.551
Ceftazidime	226 (76.6)	67 (77.0)	73 (77.7)	86 (75.4)	0.926
Piperacillin-tazobactam	193 (65.4)	57 (65.5)	64 (68.1)	72 (63.2)	0.758
Ticarcillin-clavulanate	99 (33.6)	23 (26.4)	37 (39.4)	39 (34.2)	0.181
Ciprofloxacin	211 (71.5)	70 (80.5)	63 (67.0)	78 (68.4)	0.087
Aztreonam	167 (56.6)	57 (65.5)	52 (55.3)	58 (50.8)	0.111
Colistin	294 (99.7)	87 (100)	94 (100)	113 (99.1)	1.000

Values are presented as number of patients (%).

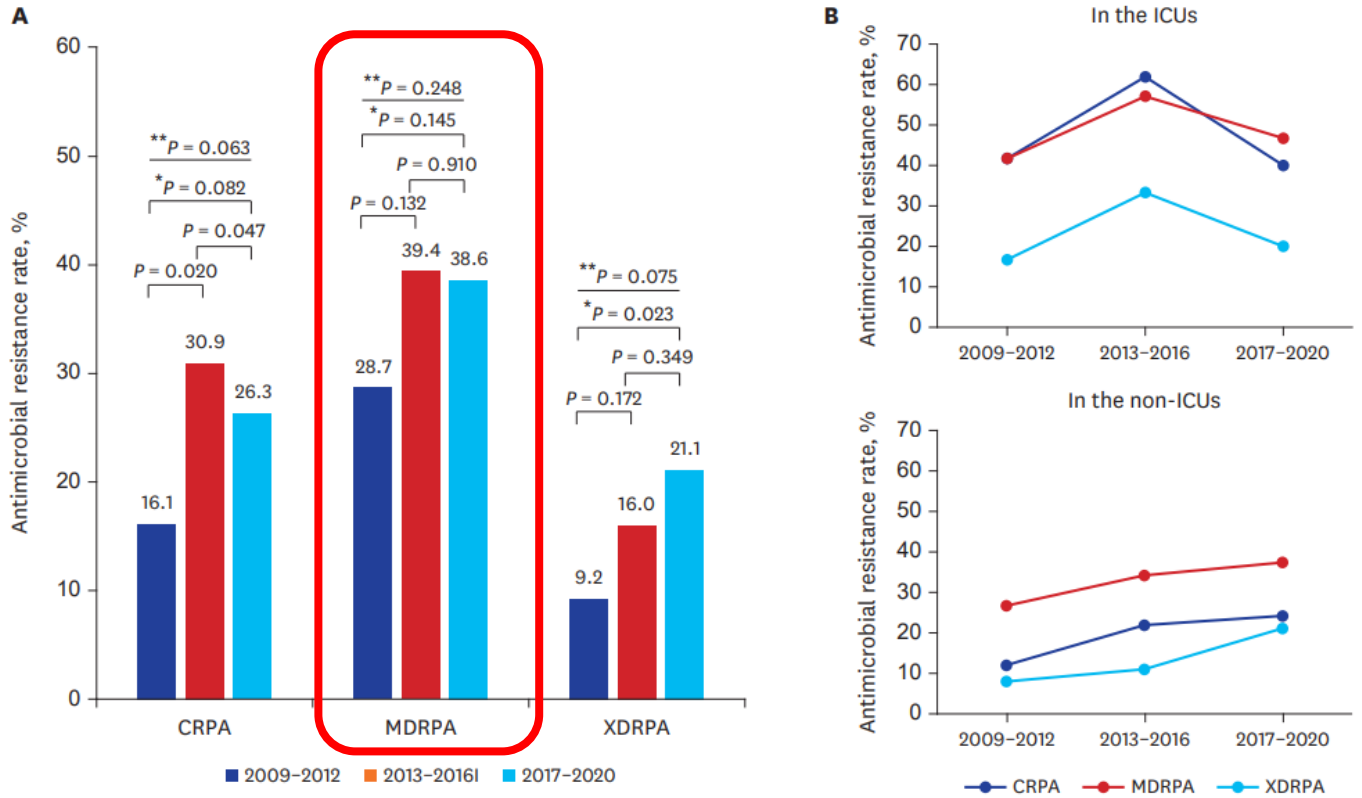

Fig. 3. Antimicrobial resistance trends in *P. aeruginosa* bacteremia. (**A**) Antimicrobial resistance rates in *P. aeruginosa* bacteremia. (**B**) Comparison of antibiotic resistance rates of the ICUs vs. the non-ICUs setting.
CRPA = carbapenem-resistant *P. aeruginosa*, MDRPA = multidrug-resistant *P. aeruginosa*, XDRPA = extensively drug-resistant *P. aeruginosa*, ICU = intensive care unit.
*Comparison between 2009–2013 and 2017–2020; **Comparison of the three groups.

국내

1) CRPA : when resistance or intermediate resistance was confirmed with one or more carbapenems having antipseudomonal activity
2) MDRPA : when the organism was not susceptible to one or more agents in at least three antimicrobial categories
3) XDRPA : when the organism was not susceptible to at least one agent in all but two or fewer antimicrobial categories
4) pandrug-resistant P. aeruginosa (PDRPA) : when the organism was not susceptible to all antimicrobial categories

J Korean Med Sci. 2021 Oct 25;36(41):e251
https://doi.org/10.3346/jkms.2021.36.e251
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Emergency & Critical Care Medicine

Check for updates

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

OPEN ACCESS

Received: May 24, 2021
Accepted: Aug 23, 2021

Address for Correspondence:
Sang-Bum Hong, MD
Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
E-mail: sbhong@amc.seoul.kr

Yong Pil Chong, MD
Department of Infectious Disease, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea.
E-mail: drchong@amc.seoul.kr

Youjin Chang [1*], Kyeongman Jeon [2*], Sang-Min Lee [3], Young-Jae Cho [4], Young Sam Kim [5], Yong Pil Chong [6], and Sang-Bum Hong [7]

[1]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, College of Medicine Inje University Sanggye Paik Hospital, Seoul, Korea
[2]Division of Pulmonary and Critical Care Medicine, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[3]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea
[4]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital, Seongnam, Korea
[5]Division of Pulmonology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[6]Department of Infectious Diseases, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[7]Department of Pulmonary and Critical Care Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

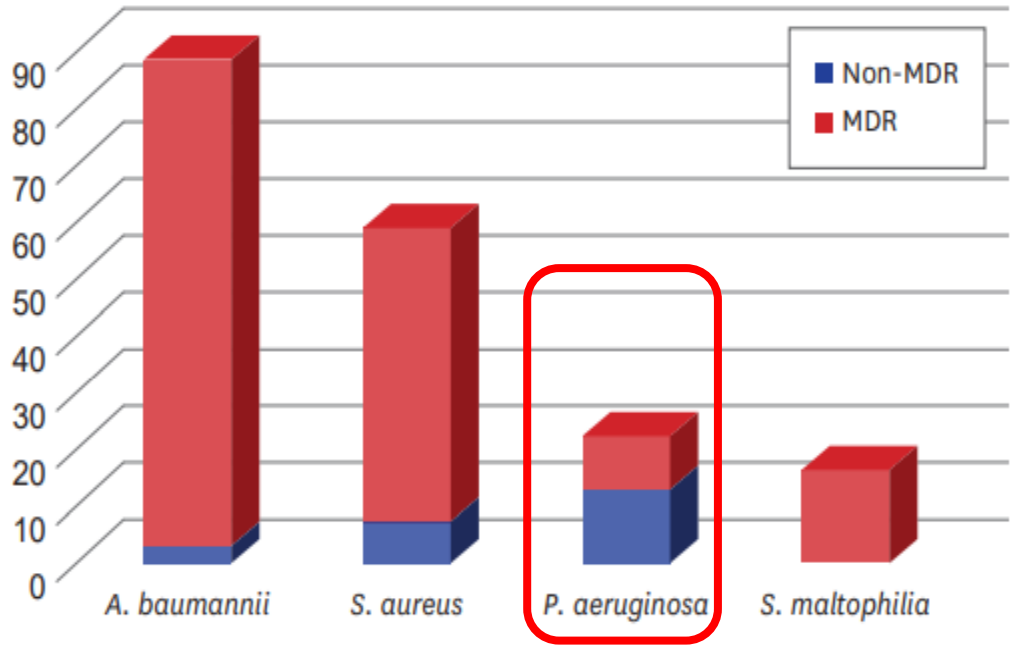

Fig. 1. Ratio of MDR bacteria in each major group of bacterial pathogens.
MDR = multidrug-resistant.

A multicenter prospective observational cohort study was conducted among patients with HAP/VAP admitted to the medical intensive care unit of 5 tertiary referral centers between August 2012 and June 2015

J Korean Med Sci. 2021 Oct 25;36(41):e251

국내

Micek et al. Critical Care (2015) 19:219
DOI 10.1186/s13054-015-0926-5

CRITICAL CARE

RESEARCH Open Access

An international multicenter retrospective study of *Pseudomonas aeruginosa* nosocomial pneumonia: impact of multidrug resistance

Scott T Micek[1*], Richard G Wunderink[2], Marin H Kollef[3], Catherine Chen[3], Jordi Rello[4], Jean Chastre[5], Massimo Antonelli[6], Tobias Welte[7], Bernard Clair[8], Helmut Ostermann[9], Esther Calbo[10], Antoni Torres[11], Francesco Menichetti[12], Garrett E Schramm[13] and Vandana Menon[14]

Table 3 Antibiotic susceptibility by country

Antibiotic class	France	Germany	Italy	Spain	United States
Aminoglycosides	141(76.6)	120 (58.3)	101 (75.2)	112 (58.9)	257 (80.2)
Antipseudomonal carbapenems	139 (60.4)	119 (52.1)	107 (57.9)	112 (47.3)	257 (79.0)
Antipseudomonal cephalosporins	140 (77.1)	120 (60.8)	101 (74.3)	111 (59.5)	258 (81.4)
Antipseudomonal fluoroquinolones	138 (66.7)	118 (61.0)	100 (75.0)	111 (52.3)	257 (75.9)
Antipseudomonal penicillins + β-lactamase inhibitors	141 (64.5)	118 (46.5)	108 (70.3)	110 (63.6)	253 (82.6)
Multidrug-resistant	141 (33.3)	120 (44.2)	108 (22.2)	113 (43.4)	258 (20.5)
Extensively drug-resistant	141 (17.7)	120 (34.2)	108 (2.8)	113 (13.3)	258 (3.5)

Data presented as number of isolates tested (% susceptible). Multidrug-resistant: non-susceptible to one or more agents in three or more antibiotic classes. Extensively drug-resistant: non-susceptible to one or more agents in all but two or fewer antibiotic classes.

Micek et al. Critical Care (2015) 19:219

Role of combination therapy versus monotherapy – definitive

HAP/VAP

Empiric/Definitive -VAP

Optimal management therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia: An observational, multicenter study comparing monotherapy with combination antibiotic therapy*

Jose Garnacho-Montero, MD, PhD; Marcio Sa-Borges, MD; Jordi Sole-Violan, MD; Fernando Barcenilla, MD; Ana Escoresca-Ortega, MD; Miriam Ochoa, MD; Aurelio Cayuela, MD, PhD, MPH; Jordi Rello, MD, PhD

Objective: To evaluate whether one antibiotic achieves equal outcomes compared with combination antibiotic therapy in patients with *Pseudomonas aeruginosa* ventilator-associated pneumonia.

Design: A retrospective, multicenter, observational, cohort study.

Setting: Five intensive care units in Spanish university hospitals.

Patients: Adult patients identified to have monomicrobial episodes of ventilator-associated pneumonia with significant quantitative respiratory cultures for *P. aeruginosa.*

2002-2005

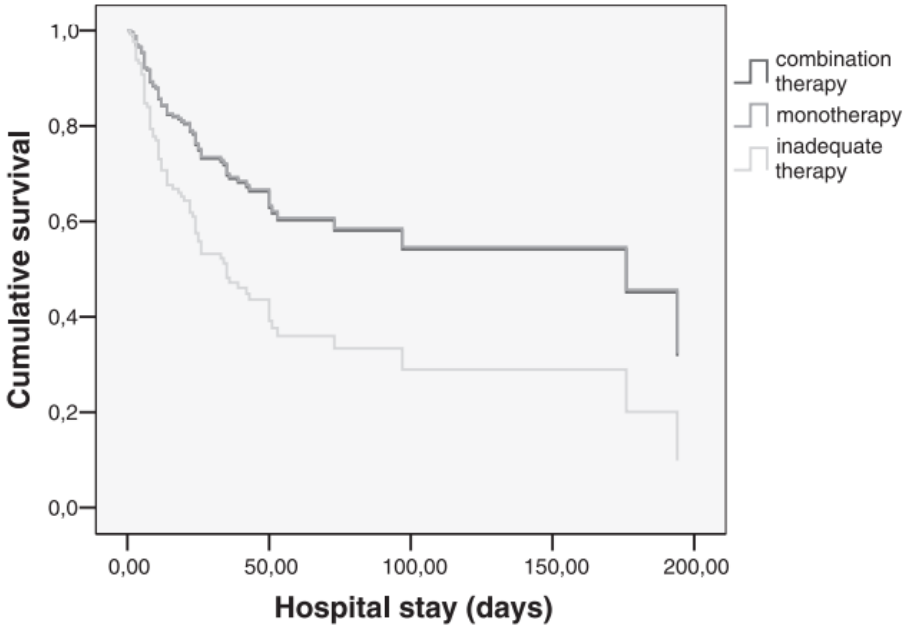

Figure 1. Cumulative survival curves of patients with inappropriate empirical antibiotic therapy compared with patients with effective monotherapy or effective combined therapy in the empirical therapy.

Table 5. Variables independently associated with mortality using Cox proportional regression analysis

	aHR	95% CI	*p*
Age	1.02	1.01–1.04	.005
Chronic cardiac failure	1.90	1.04–3.47	.035
Effective empirical therapy			.02
Combined therapy	1		
Monotherapy	0.90	0.50–1.63	.73
Inappropriate therapy	1.85	1.07–3.10	.02

aHR, adjusted hazard ratio; CI, confidence interval.

Crit Care Med 2007 Vol. 35, No. 8

De-escalation – VAP

INFECTIOUS DISEASES, 2017
VOL. 49, NO. 5, 396–404
http://dx.doi.org/10.1080/23744235.2016.1277035

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Impact of combination therapy and early de-escalation on outcome of ventilator-associated pneumonia caused by *Pseudomonas aeruginosa*

Laurène Deconinck[a], Agnès Meybeck[a], Pierre Patoz[b], Nicolas Van Grunderbeeck[c], Nicolas Boussekey[c], Arnaud Chiche[c], Pierre-Yves Delannoy[c], Hugues Georges[c] and Olivier Leroy[c]

[a]Service Universitaire des Maladies Infectieuses et du Voyageur, Centre Hospitalier de Tourcoing, Tourcoing, France; [b]Laboratoire de microbiologie, Centre Hospitalier de Tourcoing, Tourcoing, France; [c]Service de réanimation, Centre Hospitalier de Tourcoing, Tourcoing, France

Table 3. Risk factors for ICU mortality.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Characteristics at ICU admission				
Female sex	0.91 (0.41–2.04)	0.83		
Age (/5 years)	1.12 (0.98–1.29)	0.09		
Comorbidities	1.12 (0.27–4.68)	0.88		
Characteristics upon PAVM onset				
SAPS II ≥40 versus <40	3.08 (1.36–6.99)	<0.01	2.58 (1.13–5.88)	0.02
Shock	4.71 (2.03–10.89)	<0.01	4.31 (1.74–10.71)	<0.01
Multiresistant strains	1.15 (0.55–2.39)	0.71		
Empirical antibiotherapy				
Start <24 h	1.08 (0.44–2.62)	0.87		
Guided by previous endotracheal aspirate	0.89 (0.43–1.86)	0.76		
Combination versus monotherapy	0.84 (0.34–2.03)	0.69	1.53 (0.46–5.09)	0.49
Use of aminoglycoside	1.07 (0.52–2.19)	0.85		
Use of fluoroquinolone	1.02 (0.44–2.36)	0.96		
Appropriate initial antibiotherapy	0.81 (0.28–2.32)	0.70		
De-escalation	0.72 (0.33–1.56)	0.41	0.71 (0.31–1.62)	0.41

Between 1994 and 2014, all 100 patients with VAP caused by P. aeruginosa in our intensive care unit (ICU) were included in a retrospective cohort study to evaluate the prognostic impact of initial combination antibiotic therapy, France

Infectious diseases, 2017, vol 49, no.5, 396-404

Role of combination therapy versus monotherapy – definitive

bacteremia

Antimicrobial Agents and Chemotherapy®

EPIDEMIOLOGY AND SURVEILLANCE

Results from a 13-Year Prospective Cohort Study Show Increased Mortality Associated with Bloodstream Infections Caused by *Pseudomonas aeruginosa* Compared to Other Bacteria

Joshua T. Thaden,[a] Lawrence P. Park,[a] Stacey A. Maskarinec,[a] Felicia Ruffin,[a] Vance G. Fowler, Jr.,[a] David van Duin[b]

Duke University Division of Infectious Diseases, Durham, North Carolina, USA[a]; University of North Carolina Chapel Hill Division of Infectious Diseases, Chapel Hill, North Carolina, USA[b]

prospectively ascertained cohort of 2,659 hospitalized patients with BSI
over a 13-year period from a single center in USA

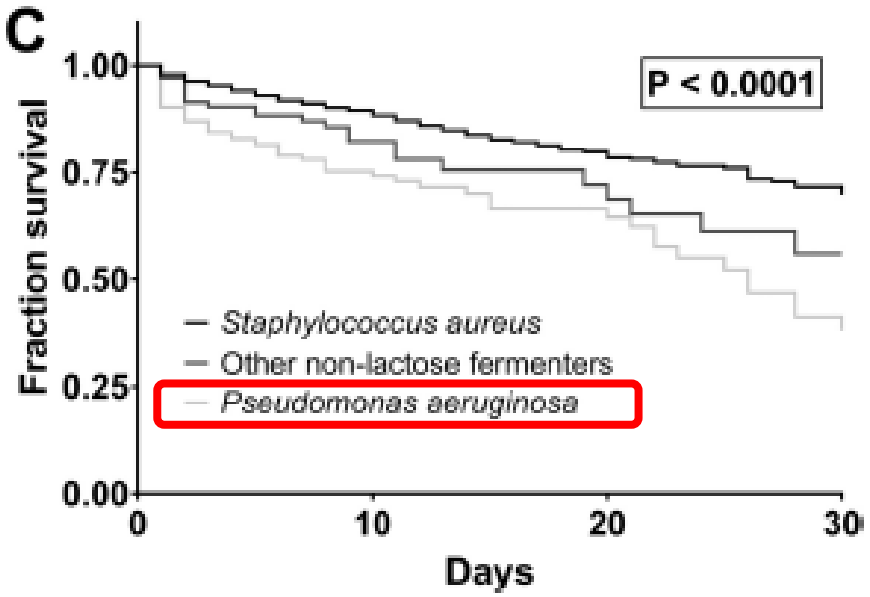

TABLE 4 Multivariable Cox regression analysis of clinical and bacterial factors influencing *Staphylococcus aureus* and Gram-negative bloodstream infection mortality in inpatients at Duke University Medical Center from 2002 to 2015[a]

Parameter	Hazard ratio	95% CI	*P*
Age	1.376	1.286–1.475	**<0.0001**
Female gender	1.129	0.936–1.359	0.203
Race[b]			
Black	1.223	0.991–1.501	0.058
Other	0.804	0.485–1.253	0.366
Pseudomonas aeruginosa BSI	1.435	1.043–1.933	**0.021**
APACHE-II chronic health score	1.168	1.101–1.244	**<0.0001**
MDR	1.051	0.869–1.269	0.609
Appropriate antibiotic therapy[c]	1.435	0.967–2.202	0.085
Days to line removal[d]			
1	0.537	0.192–1.305	0.194
2	0.606	0.232–1.424	0.271
≥3	0.904	0.259–2.468	0.857
No line-associated infection	7.227	0.392–37.881	0.060
BSI era (2005-2015)[e]	2.581	1.863–3.690	**<0.0001**
BSI source[f]			
Biliary	0.607	0.303–1.105	0.127
Pneumonia	2.264	1.628–3.169	**<0.0001**
Line	5.411	0.299–26.650	0.103
Skin/soft tissue	0.531	0.322–0.847	**0.010**
Abscess	0.721	0.387–1.254	0.273
Other	1.035	0.726–1.476	0.850
Source not identified	2.073	1.549–2.810	**<0.0001**

[a]Abbreviations: BSI, bloodstream infection; CI, confidence interval; MDR, multidrug resistant. Statistically significant values are indicated in boldface.
[b]The reference group was composed of white patients.
[c]This is a time-dependent variable in which "no appropriate antibiotic therapy" is the reference.
[d]The reference group is composed of patients with line-associated infections and line removal on day 0.
[e]The reference group is composed of BSI from 2002 to 2004.
[f]The reference group is BSI from a urine/pyelonephritis source.

Antimicrob Agents Chemother 2017; 61: e02671-16

J Korean Med Sci. 2021 Nov 8;36(43):e273
https://doi.org/10.3346/jkms.2021.36.e273
eISSN 1598-6357·pISSN 1011-8934

JKMS

Original Article
Infectious Diseases, Microbiology & Parasitology

Check for updates

Antimicrobial Susceptibility Trends and Risk Factors for Antimicrobial Resistance in *Pseudomonas aeruginosa* Bacteremia: 12-Year Experience in a Tertiary Hospital in Korea

retrospectively reviewed the medical records of patients with P. aeruginosa bacteremia admitted to Inje University Busan Paik Hospital, Busan from January 2009 to October 2020

Table 4. Risk factors for 30-day mortality in patients with *P. aeruginosa* bacteremia

Characteristics	Non-survivor (n = 80)	Survivor (n = 215)	Univariable HR (95% CI)	*P*	Multivariable HR (95% CI)	*P*
Age ≥ 65	49 (61.3)	128 (59.5)	1.2 (0.8–1.9)	0.418		
Male sex	59 (73.8)	138 (64.2)	0.7 (0.4–1.1)	0.146		
Underlying conditions						
Cardiovascular disease	9 (11.3)	21 (9.8)	1.0 (0.5–1.9)	0.892		
Cerebrovascular accident	5 (6.3)	35 (16.3)	0.3 (0.1–0.9)	0.021		
Chronic kidney disease	10 (12.5)	14 (6.5)	1.5 (0.8–3.0)	0.206		
COPD or chronic lung disease	2 (2.5)	5 (2.3)	1.0 (0.3–4.2)	0.967		
Dementia	1 (1.3)	13 (6.0)	0.3 (0.1–2.5)	0.294		
Diabetes	26 (32.5)	58 (27.0)	1.2 (0.8–2.0)	0.384		
Heart failure	5 (6.3)	9 (4.2)	1.9 (0.7–4.6)	0.183		
Hypertension	27 (33.8)	85 (39.5)	0.8 (0.5–1.2)	0.270		
Liver disease	3 (3.8)	9 (4.2)	0.9 (0.3–2.9)	0.882		
Solid cancer	44 (55.0)	111 (51.6)	1.1 (0.7–1.8)	0.518		
Hematologic malignancy	16 (20.0)	10 (4.7)	2.8 (1.6–4.9)	< 0.001	2.3 (1.3–4.0)	0.005
Immunosuppressive therapy	35 (43.8)	67 (31.2)	1.5 (0.9–2.3)	0.071		
Neutropenia	28 (35.0)	26 (12.1)	2.7 (1.7–4.3)	< 0.001		
Transplantation	2 (2.5)	5 (2.3)	1.1 (0.3–4.3)	0.931		
CCI score ≥ 5	49 (61.3)	121 (56.3)	1.2 (0.8–1.9)	0.439		
Healthcare-associated infection	65 (81.3)	180 (83.7)	0.8 (0.5–1.4)	0.400		
Previous surgery within 90 days	20 (25.0)	46 (21.4)	1.1 (0.7–1.9)	0.587		
Any antibiotic exposure within 90 days	65 (81.3)	156 (72.6)	1.3 (0.7–2.2)	0.397		
Colonization with MDROs						
CRE	1 (1.3)	3 (1.4)	1.6 (0.2–11.6)	0.638		
ESBL	4 (5.0)	23 (10.7)	0.5 (0.2–1.2)	0.126		
MRAB	9 (11.3)	7 (3.3)	2.0 (1.0–4.1)	0.049		
MRSA	2 (2.5)	3 (1.4)	1.2 (0.3–5.2)	0.738		
VRE	9 (11.3)	10 (4.7)	1.8 (0.9–3.6)	0.095		

Characteristics	Non-survivor (n = 80)	Survivor (n = 215)	Univariable HR (95% CI)	*P*	Multivariable HR (95% CI)	*P*
ICU stay	25 (31.3)	23 (10.7)	2.3 (1.5–3.8)	< 0.001	1.7 (1.1–2.8)	0.025
Devices during time at risk						
Central venous catheter	35 (43.8)	72 (33.5)	1.2 (0.8–1.9)	0.342		
Ventilator	17 (21.3)	12 (5.6)	2.6 (1.5–4.5)	< 0.001		
Indwelling urinary catheter	34 (42.5)	66 (30.7)	1.4 (0.9–2.2)	0.132		
Antimicrobial resistance						
CRPA	22 (27.5)	51 (23.7)	1.1 (0.7–1.8)	0.774		
MDRPA	28 (35.0)	78 (36.3)	0.9 (0.6–1.4)	0.669		
XDRPA	14 (17.5)	33 (15.3)	1.0 (0.6–1.8)	0.904		
Polymicrobial infection	21 (26.3)	29 (13.5)	1.8 (1.1–3.0)	0.017	1.8 (1.1–3.1)	0.032
Shock on the first day of bacteremia	56 (70.0)	28 (13.0)	8.5 (5.3–13.8)	< 0.001	6.4 (3.8–10.7)	< 0.001
Primary site of infection						
Hepato-biliary tract	15 (18.8)	64 (29.8)	0.6 (0.4–1.1)	0.096		
Gastrointestinal tract	7 (8.8)	12 (5.6)	1.2 (0.7–3.3)	0.283		
Respiratory tract	35 (43.8)	34 (15.8)	3.4 (2.2–5.2)	< 0.001	1.7 (1.0–2.8)	0.034
Urinary tract	7 (8.8)	43 (20.0)	0.4 (0.2–0.9)	0.023		
Central venous catheter	7 (8.8)	32 (14.9)	0.5 (0.2–1.1)	0.088		
Skin and soft tissue	2 (2.5)	10 (4.7)	0.5 (0.1–2.1)	0.372		
Surgical site	1 (1.3)	1 (0.5)	3.3 (0.5–23.7)	0.239		
Primary bloodstream	6 (7.5)	19 (8.8)	0.9 (0.4–2.1)	0.824		
Invasive drainage procedures	9 (11.3)	53 (24.7)	0.5 (0.2–0.9)	0.024		
Active antimicrobial therapy	67 (83.8)	177 (82.3)	0.7 (0.4–1.3)	0.292		
Concordant empirical antimicrobial therapy	56 (70.0)	125 (58.1)	1.4 (0.9–2.3)	0.141		
Single antibiotics	42 (52.5)	109 (50.7)				
Aminoglycoside	0 (0)	6 (2.8)				
Anti-pseudomonal cephalosporine	12 (15.0)	23 (10.7)				
Anti-pseudomonal penicillin	5 (6.3)	39 (18.1)				
Carbapenem	17 (21.3)	31 (14.4)				
Fluoroquinolone	1 (1.3)	8 (3.7)				
Colistin	7 (8.8)	2 (0.9)				
Combination antibiotics	14 (17.5)	16 (7.4)				
Anti-pseudomonal cephalosporine + aminoglycoside	1 (1.3)	2 (0.9)				
Anti-pseudomonal cephalosporine + fluoroquinolone	1 (1.3)	1 (0.5)				
Anti-pseudomonal penicillin + fluoroquinolone	9 (11.3)	12 (5.6)				
Carbapenem + aminoglycoside	2 (2.5)	0 (0)				
Carbapenem + fluoroquinolone	1 (1.3)	1 (0.5)				

Values are presented as number (%).
HR = hazard ratio, CI = confidence interval, COPD = chronic obstructive pulmonary disease, CCI = Charlson comorbidity index, MDRO = multidrug-resistant organism, CRE = carbapenem-resistant *Enterobacteriaceae*, ESBL = extended-spectrum beta-lactamase-producing bacteria, MRAB = multi-drug resistant *Acinetobacter baumannii*, MRSA = methicillin-resistant *Staphylococcus aureus*, VRE = vancomycin-resistant *Enterococcus*, ICU = intensive care unit, CRPA = carbapenem-resistant *P. aeruginosa*, MDRPA = multidrug-resistant *P. aeruginosa*, XDRPA = extensively drug-resistant *P. aeruginosa*.

국내

J Korean Med Sci. 2021 Nov 8;36(43):e273

MAJOR ARTICLE

Empiric/Definitive -bacteremia

Effect of Adequate Single-Drug vs Combination Antimicrobial Therapy on Mortality in *Pseudomonas aeruginosa* Bloodstream Infections: A Post Hoc Analysis of a Prospective Cohort

Carmen Peña,[1] Cristina Suarez,[1] Alain Ocampo-Sosa,[2] Javier Murillas,[3] Benito Almirante,[4] Virginia Pomar,[5] Manuela Aguilar,[6] Ana Granados,[7] Esther Calbo,[8] Jesús Rodríguez-Baño,[9] Fernando Rodríguez,[10] Fe Tubau,[1] Antonio Oliver,[3] and Luis Martínez-Martínez[2,11]; for the Spanish Network for Research in Infectious Diseases (REIPI)

[1]Servicio de Enfermedades Infecciosas, Hospital Universitario de Bellvitge–IDIBELL, Barcelona; [2]Servicio de Microbiología, Hospital Universitario Marqués de Valdecilla–IFIMAV, Santander; [3]Servicio de Microbiología y Unidad de Enfermedades Infecciosas, Hospital Universitario de Son Espases, Palma de Mallorca; [4]Servicio de Enfermedades Infecciosas, Hospital Universitario Vall d'Hebrón, [5]Unidad de Enfermedades Infecciosas, Hospital Santa Creu i Sant Pau, Barcelona; [6]Servicio de Enfermedades Infecciosas, Hospital Universitario Virgen del Rocío, Sevilla; [7]Sección de Enfermedades Infecciosas, Consorci Hospitalari Parc Taulí, Sabadell; [8]Sección de Enfermedades Infecciosas, Hospital Mutua de Terrasa; [9]Sección de Enfermedades Infecciosas, Hospital Universitario Virgen Macarena, Sevilla; [10]Servicio de Microbiología Infecciosas, Hospital Universitario Reina Sofía–IMIBIC, Córdoba; and [11]Departamento de Biología Molecular, Universidad de Cantabria, Santander, Spain

A post hoc analysis of patients with PA bacteremia carried out in 10 public hospitals located in 4 areas of Spain between January 2008 and December 2009

Table 3. Cox Regression Analysis of Relation Between Empirical and Definitive Antimicrobial Therapy and 30-Day Mortality

Characteristic	AHR	95% CI	*P* Value
Empirical antimicrobial therapy			
AECT	1.0 (reference)		
AESD	1.17	.70–1.96	.54
IET	1.70	.99–2.92	.052
Definitive antimicrobial therapy			
ADCT	1.0 (reference)		
ADSD	1.34	.73–2.47	.35
IDT	0.86	.36–2.02	.73

Abbreviations: ADCT, adequate definitive combination therapy; ADSD, adequate definitive single-drug therapy; AECT, adequate empirical combination therapy; AESD, adequate empirical single-drug therapy; AHR, adjusted hazard ratio; CI, confidence interval; IDT, inadequate definitive therapy; IET, inadequate empirical therapy.

CID 2013;57(2):208–16

Park et al. BMC Infectious Diseases 2012, 12:308
http://www.biomedcentral.com/1471-2334/12/308

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Impact of adequate empirical combination therapy on mortality from bacteremic *Pseudomonas aeruginosa* pneumonia

So-Youn Park[1], Hyun Jung Park[1], Song Mi Moon[1], Ki-Ho Park[1], Yong Pil Chong[1], Mi-Na Kim[2], Sung-Han Kim[1], Sang-Oh Lee[1], Yang Soo Kim[1], Jun Hee Woo[1] and Sang-Ho Choi[1*]

Empiric/Definitive -bacteremia

retrospective cohort study, Asan medical cencer
n=100

- The 28-day mortality was significantly higher in the inadequate therapy group than the adequate therapy group (68.6% [24/35] vs. 41.5% [27/65], p =0.01)

- Multivariate logistic regression analysis identified the absence of septic shock at the time of bacteremia (AOR, 0.07; 95% CI, 0.01-0.49; p = 0.008), and combination therapy (AOR, 0.05; 95% CI, 0.01-0.34; p = 0.002, univariate OR 0.38 (0.14-1.06)) as variables that were independently associated with decreased all-cause 28-day mortality

국내

Park et al. BMC Infectious Diseases 2012, 12:308

International Journal of Antimicrobial Agents 59 (2022) 106512

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Beta-lactam monotherapy or combination therapy for bloodstream infections or pneumonia due to *Pseudomonas aeruginosa*: a meta-analysis

Lorenzo Onorato[a], Margherita Macera[a], Federica Calò[a], Paolo Cirillo[b], Giovanni Di Caprio[b], Nicola Coppola[a,*]

[a] Department of Mental Health and Public Medicine, Section of Infectious Diseases, University of Campania, Naples, Italy
[b] Infectious Diseases Unit, AORN Sant' Anna e San Sebastiano, Caserta, Italy

Definitive – bacteremia or pneumonia

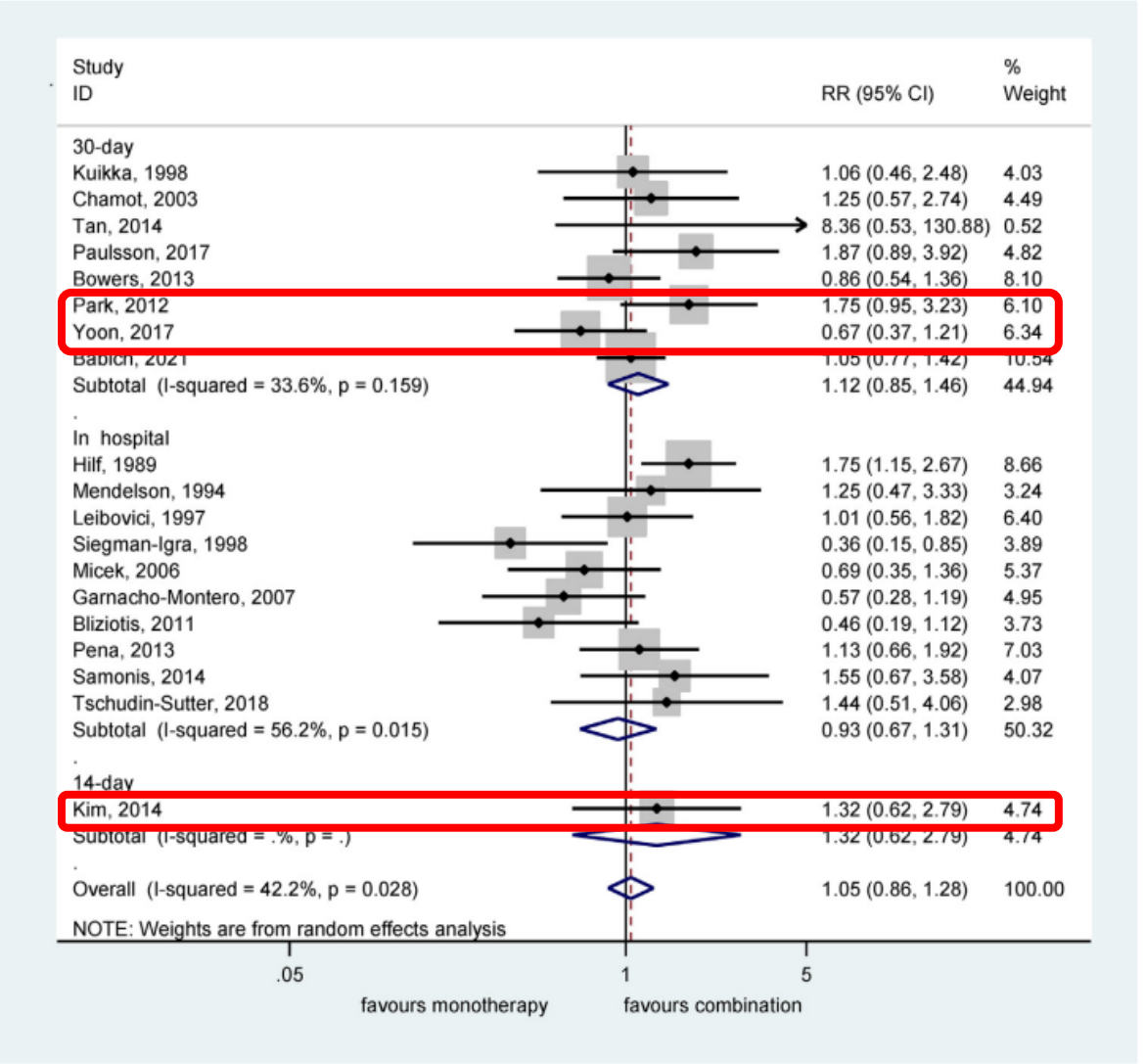

Figure 3. Forest plot of RRs of mortality in patients treated with definitive combination or monotherapy

Role of combination therapy versus monotherapy – definitive

Antibiotics selection

aminoglycoside

Table 2
Risk factors associated with 30-day mortality in patients given appropriate empiric therapy (n=58).

Variable	Univariate analysis OR (95% CI)	*P* value	Multivariate analysis[a] OR (95% CI)	*P* value
Age	1.05 (1.00–1.12)	0.06	1.11 (1.02–1.20)	0.02
Total length of hospital stay	1.00 (0.99–1.02)	0.62		
Length of hospital stay before culture	1.01 (0.99–1.03)	0.24[b]		
Comorbidities				
Congestive heart failure	3.00 (0.74–12.18)	0.12		
COPD	2.51 (0.52–12.09)	0.25		
Diabetes mellitus	1.53 (0.39–5.99)	0.55		
APACHE II	1.09 (0.99–1.19)	0.07		
Functional aminoglycoside monotherapy[c]	3.33 (0.76–14.58)	0.11	12.54 (1.51–103.99)	0.02
Source of bacteremia				
Line	1.22 (0.12–12.26)	0.87		
Urinary tract	0.30 (0.03–2.60)	0.27		
Abdomen	4.67 (1.01–21.49)	0.05		

[a] Receiver operating characteristic area under the curve = 0.784.
[b] *P* value = 0.17 with the variable log-transformed (0 day assigned a value of 1).
[c] Compared to beta-lactams.

single-center, retrospective, cohort study conducted from January 2002 through December 2015 in an 850-bed academic teaching hospital in Houston, Texas

Diagnostic Microbiology and Infectious Disease 93 (2019) 346–348

International Journal of Antimicrobial Agents 52 (2018) 451–458

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

International Journal of Antimicrobial Agents 52 (2018) 451–458

carbapenem

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

J Nicholas O'Donnell, PharmD, MSc, BCPS, Assistant Professor of Pharmacy Practice[a], Nathaniel J Rhodes, PharmD, MSc, BCPS, AQID, Assistant Professor of Pharmacy Practice[b,c], Jenna Lopez, PharmD, Clinical Pharmacist[d], Rebecca Jett, PharmD[c], Marc H Scheetz, PharmD, MSc, BCPS AQ-ID, Professor of Pharmacy Practice[c,e,f,*]

[a] Department of Pharmacy Practice, Albany College of Pharmacy and Health Sciences, Albany, NY, USA
[b] Chicago College of Pharmacy, Department of Pharmacy Practice, Midwestern University, Downers Grove, IL, USA
[c] Department of Pharmacy, Northwestern Memorial Hospital, Chicago, IL, USA
[d] Department of Pharmacy, Loyola University Medical Center, Maywood, IL, USA
[e] Chicago College of Pharmacy, Department of Pharmacy Practice, Midwestern University, Downers Grove, IL, USA
[f] College of Graduate Studies, Department of Pharmacology, Midwestern University, Downers Grove, IL, USA

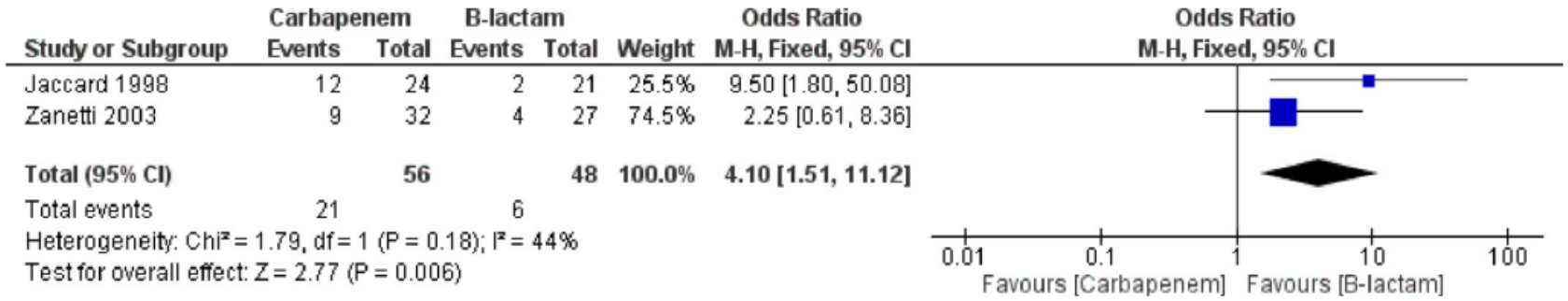

Fig. 3. Forest plot of odds ratios for clinical failure in patients with nosocomial pneumonia caused by *P. aeruginosa*

Patients treated with imipenem were more than twice as likely to experience clinical failure in pneumonia caused by P. aeruginosa (Fig. 3; OR 2.64, 95% CI 1.51-11.12, I 2=44%)

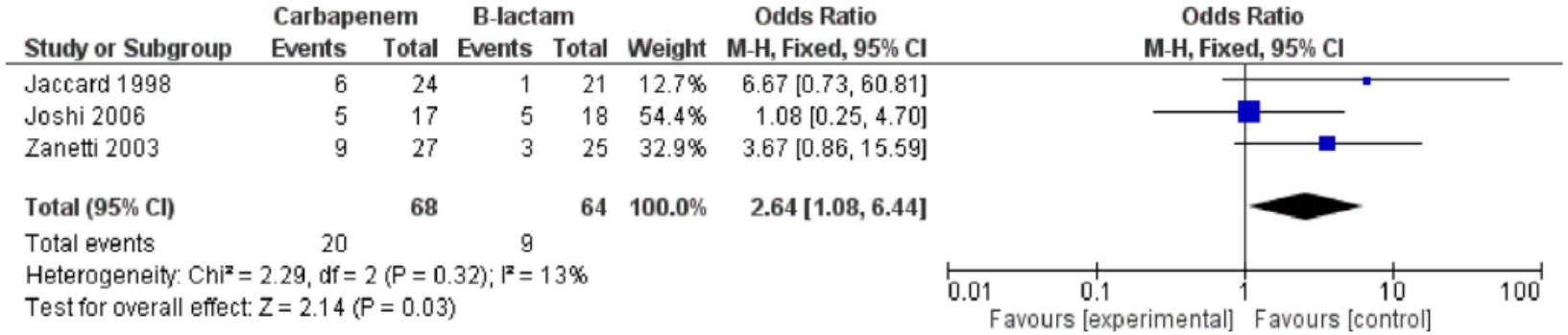

Fig. 5. Forest plot of odds ratios for development of resistance to the study drug in patients with nosocomial pneumonia caused by *P. aeruginosa*

Among patients infected with P. aeruginosa, resistance was more likely to develop in patients treated with imipenem compared with those treated with TZP or cefepime (Figure 5; OR 2.64, 95% CI 1.08-6.44, I 2=0%)

Clinical Infectious Diseases
MAJOR ARTICLE

Carbapenem - bacteremia

Ceftazidime, Carbapenems, or Piperacillin-tazobactam as Single Definitive Therapy for *Pseudomonas aeruginosa* Bloodstream Infection: A Multisite Retrospective Study

Tanya Babich,[1] Pontus Naucler,[2] John Karlsson Valik,[2] Christian G. Giske,[3] Natividad Benito,[4] Ruben Cardona,[5] Alba Rivera,[6] Celine Pulcini,[7,8] Manal Abdel Fattah,[8] Justine Haquin,[8] Alasdair Macgowan,[9] Sally Grier,[9] Julie Gibbs,[9] Bibiana Chazan,[10] Anna Yanovskay,[10] Ronen Ben Ami,[1,11] Michal Landes,[11] Lior Nesher,[12] Adi Zaidman-Shimshovitz,[12] Kate Mccarthy,[13] David L. Paterson,[13] Evelina Tacconelli,[14] Michael Buhl,[14] Susanna Mauer,[14] Jesus Rodriguez-Bano,[15] Isabel Morales,[15] Antonio Oliver,[16] Enrique Ruiz De Gopegui,[16] Angela Cano,[17] Isabel Machuca,[17] Monica Gozalo-Marguello,[18] Luis Martinez Martinez,[18] Eva M. Gonzalez-Barbera,[19] Iris Gomez Alfaro,[19] Miguel Salavert,[20] Bojana Beovic,[21] Andreja Saje,[21] Manica Mueller-Premru,[22] Leonardo Pagani,[23] Virginie Vitrat,[24] Diamantis Kofteridis,[25] Maria Zacharioudaki,[25] Sofia Maraki,[25] Yulia Weissman,[1] Mical Paul,[26] Yaakov Dickstein,[26] Leonard Leibovici,[27] and Dafna Yahav[28]

retrospective, observational, multinational, and multicenter cohort study from 25 centers in 9 countries across Europe, Australia and Israel hospitalized patients from 1 January 2009 until 31 October 2015

Table 3. Multivariate Analyses for Risk Factors for 30-day All-cause Mortality: Entire Cohort and Propensity Score–Adjusted Cohort

	Odds Ratio (95% CI)		
Variable	Univariate Analysis	Multivariate Logistic Regression Analysis (n = 767)	Multivariate Logistic Regression Analysis, Propensity Score Adjusted (n = 542)
Definitive treatment (carbapenem as reference)			
Ceftazidime	0.84 (.52–1.37)	0.92 (.5–1.67)	1.14 (.52–2.46)
Piperacillin-tazobactam	0.76 (.48–1.18)	1.17 (.69–1.67)	1.3 (.67–2.51)

Clin Infect Dis . 2020 May 23;70(11):2270-2280.

Carbapenem - bacteremia

Table 4. Secondary Outcomes According to Drug Group

Outcome	Ceftazidime (n = 213)	Piperacillin-Tazobactam (n = 344)	Carbapenem (n = 210)	Total Cohort (n = 767)	*P*
Clinical outcomes					
7-day mortality, n (%)	13 (6.1)	17 (4.9)	16 (7.6)	46 (6)	.435
Clinical failure, n/N (%)	78/170 (45.9)	114/306 (37.3)	80/180 (44.4)	272/656 (41.5)	.119
Late septic shock, n (%)	11 (5.4)	10 (3.1)	14 (7)	35 (4.8)	.110
Late need for respiratory support, n (%)	11 (5.6)	8 (2.5)	10 (5.1)	29 (4.1)	.167
Hospital duration, days					
Entire cohort (N = 721)	13 (9–23)	13 (7–24)	14 (8–28)	13 (8–24)	.363
Alive at day 30 (N = 587)	14 (9–31)	13 (8–27.5)	15 (9–38)	14 (9–31)	.16
Microbiological failure (N = 727), n/N (%)	23/205 (11.2)	37/325 (11.4)	31/196 (15.7)	91/723 (12.5)	.278
Fever duration, days					
Entire cohort (N = 641)	1 (1–3)	1 (0.75–3)	1 (1–4)	1 (1–3)	.14
Alive at day 30 (N = 526)	1 (1–3)	1 (1–2)	2 (1–4)	1 (1–3)	.094
Adverse events					
Renal failure, n (%)	(N = 195)	(N = 334)	(N = 209)	(N = 738)	.217
No	169 (86.7)	289 (86.5)	181 (86.6)	639 (86.6)	
Risk	14 (7.2)	22 (6.6)	8 (3.8)	44 (6)	
Injury	6 (3.1)	8 (2.4)	6 (2.9)	20 (2.7)	
Failure	0	7 (2.1)	9 (4.3)	16 (2.2)	
Loss	3 (1.5)	2 (0.6)	3 (1.4)	8 (1.1)	
ESKD, n (%)	3 (1.5)	6 (1.8)	2 (1)	11 (1.5)	
Any diarrhea, n/N (%)	26/204 (12.7)	55/333 (16.5)	26/209 (12.4)	107/746 (14.3)	.313
Clostridium difficile infection, n/N (%)	3/205 (1.5)	8/339 (2.4)	2/209 (1)	13/753 (1.7)	.446
Anaphylactic shock	0	0	0	0	
Any rash, n/N (%)	4/190 (2.1)	9/330 (2.7)	4/207 (1.9)	17/727 (2.3)	.813
Seizures, n/N (%)	4/191 (2.1)	5/330 (1.5)	1/207 (0.5)	10/728 (1.4)	.369
Drug discontinuation due to adverse events, n/N (%)	2/191 (1)	3/330 (0.9)	4/207 (1.9)	9/728 (1.2)	.558
New resistance profile, n/N (%)					
Resistant PA	25/201 (12.4)	28/332 (8.4)	36/206 (17.5)	89/739 (12)	.007
Resistant GNRs[a]	15/204 (7.4)	29/333 (8.7)	22/206 (10.7)	66/743 (8.9)	.491
MRSA	6/200 (3)	7/323 (2.2)	4/205 (2)	17/728 (2.3)	.756
VRE	3/202 (1.5)	4/323 (1.2)	5/206 (2.4)	12/731 (1.6)	.565

Continuous variables are presented as median (IQR) or mean ± SD according to distribution of variable; categorical variables are presented as no. (%). Definitions of secondary outcomes, including new resistance profile are presented in Appendix 3.

Abbreviations: ESKD, end-stage kidney disease; IQR, interquartile range; GNR, gram-negative rod; MRSA, methicillin-resistant *Staphylococcus aureus*; PA, *Pseudomonas aeruginosa*; SD, standard deviation; VRE, vancomycin-resistant enterococci.

[a]Gram-negative bacteria other than *Pseudomonas*.

Clin Infect Dis . 2020 May 23;70(11):2270-2280.

Pseudomonas aeruginosa Ventilator-associated Pneumonia

Predictive Factors of Treatment Failure

Benjamin Planquette[1], Jean-Francois Timsit[2,3], Benoit Y. Misset[4], Carole Schwebel[2], Elie Azoulay[5], Christophe Adrie[3,5], Aurélien Vesin[7], Samir Jamali[8], Jean-Ralph Zahar[9], Bernard Allaouchiche[10], Bertrand Souweine[11], Michael Darmon[12], Anne-Sylvie Dumenil[13], Dany Goldgran-Toledano[14], Bruno H. Mourvillier[15], and Jean-Pierre Bédos[1]; on behalf of the OUTCOMEREA Study Group*

[1]Medical Surgical ICU, André Mignot Hospital, Versailles-Le Chesnay, France; [2]University Grenoble 1, Polyvalent ICU, Albert Michallon Hospital, Grenoble, France; [3]ICU, Saint Joseph Hospital, Paris, France; [4]Medical ICU, Saint Louis Hospital, Paris, France; [5]ICU, Delafontaine Hospital, Saint Denis, France; [6]Physiology, Cochin Hospital, Paris, France; [7]University Grenoble 1, Integrated Research Center U823, Grenoble, France; [8]ICU, Dourdan Hospital, Dourdan, France; [9]Microbiology Department, Necker Hospital, Paris, France; [10]ICU, Edouard Herriot Hospital, Lyon, France; [11]ICU, Gabriel Montpied Hospital, Clermont-Ferrand, France; [12]Medical ICU, Saint Etienne University Hospital, St Etienne, France; [13]Antoine Béclère Hospital, Clamart, France; [14]Gonesse Hospital, Gonesse, France; and [15]University Paris Diderot, Medical and Infectious Diseases ICU, Bichat Claude Bernard University Hospital, Paris, France

Quinolone -VAP

From January 1997 to August 2011
retrospective analysis of observational study using data prospectively entered into a multicenter database
12 French ICUs

Characteristics	Alive without Recurrence within 14 Days ($n = 202$)	Treatment Failure within 14 Days ($n = 112$)	Univariate *P* Value	Multivariate* SHR (95% CI)	Multivariate* *P* Value
Between admission and the day of the first PA-VAP					
Aminoglycosides	93 (46)	57 (50.9)	0.4	—	—
Penems	39 (19.3)	31 (27.7)	0.05	—	—
Fosfomycin	6	2 (1.8)	0.5	—	—
Macrolides	44 (21.8)	29 (25.9)	0.3	—	—
Fluoroquinolones	49 (24.3)	40 (35.7)	0.044	2.1 (1.4–3.2)	0.0007
Ceftazidime	16 (7.9)	3 (2.7)	0.09	—	—
Ureido-carboxypenicillins	77 (38.1)	40 (35.7)	0.8	—	—
Cefpirome/cefepime	16 (7.9)	10 (8.9)	0.6	—	—
On first PA-VAP					
PA-bacteremia	2 (1)	5 (4.5)	0.003	4.1 (1.6–10.4)	0.003
Delay to first PA-VAP onset < 12 d	97 (48)	54 (48.2)	0.9	—	—
Susceptibility of pathogen, resistant/multiresistant†	83 (41.1)	52 (46.4)	0.4	—	—
Prescribed treatments					
Aminoglycosides	150 (74.3)	82 (73.2)	0.8	—	—
Penems	69 (34.2)	49 (43.8)	0.09	—	—
Fosfomycin	17 (8.4)	9 (8)	0.9	—	—
Macrolides	34 (16.8)	19 (17)	0.9		
Fluoroquinolones	88 (43.6)	35 (31.3)	0.02	0.5 (0.3–0.7)	0.0006
Ceftazidime	76 (37.6)	41 (36.6)	0.8	—	—
Ureido-carboxypenicillins	114 (56.4)	55 (49.1)	0.3	—	—
Cefpirome/cefepime	25 (12.4)	7 (6.3)	0.11	—	—
Initial adequate treatment					
None	33 (16.3)	20 (17.9)	0.6	—	—
Monotherapy	55 (27.2)	35 (31.3)		—	
Bitherapy/tritherapy	114 (56.4)	57 (50.9)			
Timing of adequate treatment‡					
Delayed	73 (36)	21 (30.9)	0.8	—	
Early	130 (64)	47 (69.1)		—	

Am J Respir Crit Care Med Vol 188, Iss. 1, pp 69–76, Jul 1, 2013

Raman et al. Antimicrobial Resistance and Infection Control (2018) 7:79
https://doi.org/10.1186/s13756-018-0370-9

Antimicrobial Resistance and Infection Control

RESEARCH Open Access

Risk factors for hospitalized patients with resistant or multidrug-resistant *Pseudomonas aeruginosa* infections: a systematic review and meta-analysis

Gowri Raman[1*], Esther E. Avendano[1], Jeffrey Chan[1], Sanjay Merchant[2] and Laura Puzniak[2]

quinolone/carbapenem

MDR Risk

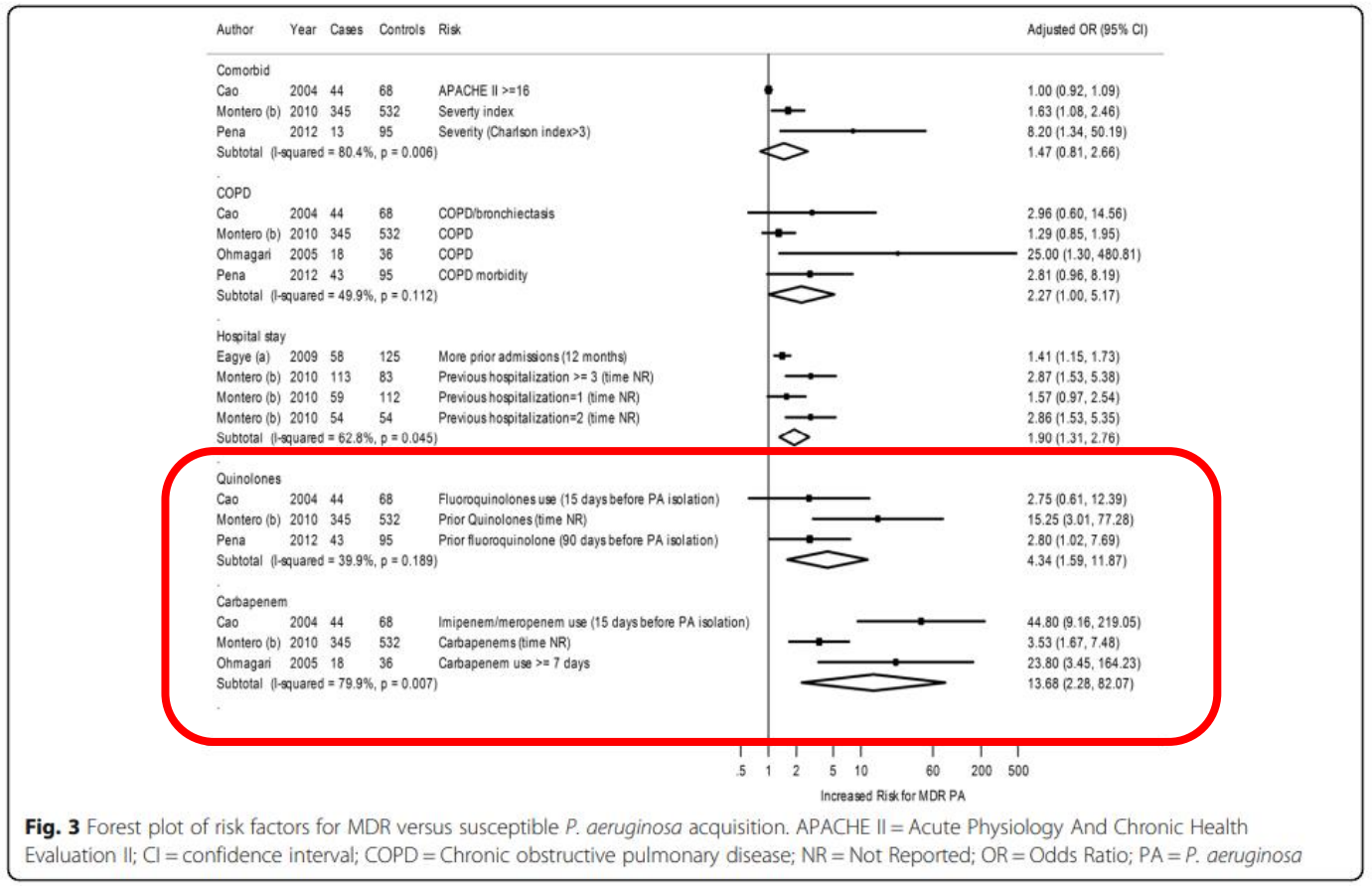

Fig. 3 Forest plot of risk factors for MDR versus susceptible *P. aeruginosa* acquisition. APACHE II = Acute Physiology And Chronic Health Evaluation II; CI = confidence interval; COPD = Chronic obstructive pulmonary disease; NR = Not Reported; OR = Odds Ratio; PA = *P. aeruginosa*

Raman et al. Antimicrobial Resistance and Infection Control (2018) 7:79

Ciprofloxacin combination - bacteremia

Eur J Clin Microbiol Infect Dis (2017) 36:1187–1196
DOI 10.1007/s10096-017-2907-x

ORIGINAL ARTICLE

Antimicrobial combination treatment including ciprofloxacin decreased the mortality rate of *Pseudomonas aeruginosa* bacteraemia: a retrospective cohort study

M. Paulsson[1] · A. Granrot[2] · J. Ahl[2] · J. Tham[2] · F. Resman[1,2] · K. Riesbeck[1] · F. Månsson[2]

All cases of P. aeruginosa bacteraemia (n = 292) in southwest Skåne County, Sweden (years 2005–2010, adult population 361,112) and the whole county (2011–2012, 966,130) were identified. Available medical and microbiological records for persons aged 18 years or more were reviewed (n = 235)

Table 3 The antimicrobial treatment choice influences 30-day mortality

	30-Day mortality, empirical treatment ($n = 219$)					
	n	Died (%)	OR (95%)	*p*-value	adj. OR (95% CI)	adj. *p*-value
Cefotaxime or cefuroxime	100	23 (23.0)	1.06 (0.56–2.00)	0.87	0.68 (0.31–1.49)	0.34
Benzylpenicillin	8	4 (50.0)	3.51 (0.85–14.42)	0.08	3.09 (0.52–18.38)	0.22
Imipenem or meropenem	34	5 (14.7)	0.55 (0.20–1.51)	0.25	0.84 (0.23–3.12)	0.79
Piperacillin–tazobactam	37	7 (18.9)	0.78 (0.32–1.90)	0.58	0.61 (0.20–1.89)	0.39
Ciprofloxacin	11	1 (9.1)	0.33 (0.04–2.64)	0.30	0.57 (0.06–5.56)	0.63
Combination including tobramycin	40	10 (25.0)	1.20 (0.54–2.66)	0.66	1.10 (0.39–3.11)	0.85
Any other combination	39	6 (15.4)	0.58 (0.23–1.48)	0.30	0.40 (0.13–1.27)	0.12
No empirical antibiotic treatment	15	8 (53.3)	4.52 (1.55–13.20)	0.007	**5.84 (1.43–23.84)**	**0.01**
Adequate antipseudomonal treatment	104	16 (15.4)	0.45 (0.23–0.88)	0.02	**0.37 (0.16–0.89)**	**0.03**
	30-Day mortality, definitive treatment ($n = 203$)					
	n	Died (%)	OR (95% CI)	*p*-value	adj. OR (95% CI)	adj. *p*-value
Cefotaxime or cefuroxime	10	4 (40.0)	3.93 (1.04–14.81)	0.043	5.59 (0.94–33.35)	0.06
Imipenem or meropenem	43	5 (11.6)	0.65 (0.23–1.80)	0.41	1.26 (0.35–4.49)	0.73
Piperacillin–tazobactam	67	11 (16.4)	1.05 (0.47–2.32)	1.00	1.07 (0.40–2.87)	0.89
Ceftazidime	21	1 (4.8)	0.24 (0.03–1.88)	0.18	0.19 (0.02–1.91)	0.16
Ciprofloxacin, monotherapy	25	2 (8.0)	0.43 (0.10–1.92)	0.27	0.32 (0.06–1.83)	0.20
Combination including ciprofloxacin	78	5 (6.4)	0.25 (0.09–0.68)	0.006	**0.16 (0.05–0.55)**	**0.003**
Combination including tobramycin	35	4 (11.4)	0.65 (0.21–1.97)	0.44	1.23 (0.31–4.91)	0.77
Adequate antipseudomonal treatment	174	20 (11.5)	0.17 (0.07–0.41)	<0.001	**0.17 (0.05–0.62)**	**0.007**

The effect of empiric and definitive antimicrobial treatment on 30-day mortality. Correlations to 30-day mortality presented as odds ratio (*OR*) with 95% confidence interval (*95% CI*) and *p*-values. The multivariable model contained age, sex, lung disease, vascular graft, peripheral vascular disease, chemotherapy in the last 6 months, metastasis, haematological disease, diabetes mellitus and neurological paresis, coinfections, treatment in the intensive care unit, tracheal intubation and urinary catheter. Significant adjusted *p*-values are in **bold**. Treatment regimens given to less than five patients are not shown in this table

Eur J Clin Microbiol Infect Dis (2017) 36:1187–1196

Role of combination therapy versus monotherapy – definitive

MDR

International Journal of Antimicrobial Agents 57 (2021) 106344

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

In vitro

Review

Systematic review and meta-analysis of in vitro efficacy of antibiotic combination therapy against carbapenem-resistant Gram-negative bacilli

Luigia Scudeller[a,1], Elda Righi[b,1,*], Margherita Chiamenti[b], Damiano Bragantini[b], Giulia Menchinelli[c,d], Paolo Cattaneo[b], Christian G. Giske[e], Thomas Lodise[f], Maurizio Sanguinetti[c,d], Laura J.V. Piddock[g], François Franceschi[g], Sally Ellis[g], Elena Carrara[b], Alessia Savoldi[b], Evelina Tacconelli[b,h,i,*]

[a] Clinical Epidemiology and Biostatistics, IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano Foundation, Milan, Italy
[b] Division of Infectious Diseases, Department of Diagnostic and Public Health, University of Verona, P.le L.A. Scuro 10, 37134 Verona, Italy
[c] Dipartimento di Scienze Biotecnologiche di Base, Cliniche Intensivologiche e Perioperatorie, Università Cattolica del Sacro Cuore, Rome, Italy
[d] Dipartimento di Scienze di Laboratorio e Infettivologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy
[e] Clinical Microbiology, Karolinska University Hospital and Karolinska Institutet, Stockholm, Sweden
[f] Albany College of Pharmacy and Health Sciences, Albany, New York, USA
[g] Global Antibiotic Research & Development Partnership (GARDP), 15 Chemin Louis-Dunant, Geneva, Switzerland
[h] Division of Infectious Diseases, Department of Internal Medicine I, German Center for Infection Research, University of Tübingen, Otfried Müller Straße 12, 72074 Tübingen, Germany
[i] German Centre for Infection Research (DZIF), Clinical Research Unit for Healthcare Associated Infections, Tübingen, Germany

Table 4
In vitro synergy of antibiotic combinations against *Pseudomonas aeruginosa* assessed by pharmacokinetic/pharmacodynamic (PK/PD) and time–kill (TK) studies

Antibiotic regimen	Assay	No. of strains	No. of studies	No. of tests	ES	95% CI	Synergy rate
Ceftazidime/avibactam + amikacin	PK/PD	3	1	1	0.33	0.06–0.79	Low
Colistin + doripenem	PK/PD	3	2	6	0.57	0.03–1.00	Moderate
Imipenem + amikacin	PK/PD	1	1	2	1.00	0.21–1.00	High
Ceftolozane/tazobactam + colistin	TK	4	1	1	0.50	0.15–0.85	Moderate
Ceftolozane/tazobactam + aztreonam	TK	4	1	1	0.00	0.00–0.49	No synergy
Ceftolozane/tazobactam + amikacin	TK	4	1	1	0.00	0.00–0.49	No synergy
Colistin + imipenem	TK	2	1	2	0.67	0.08–1.00	Moderate
Colistin + meropenem	TK	7	1	4	0.43	0.16–0.75	Moderate
Imipenem + amikacin	TK	87	4	7	0.35	0.23–0.47	Low
Imipenem + tobramycin	TK	2	1	8	0.39	0.04–0.80	Moderate
Meropenem + amikacin	TK	63	2	1	0.43	0.31–0.55	Moderate

ES, effect size; CI, confidence interval.
NOTE: Pooled synergy or antagonism rate was defined based on the ES as follows: high, ES $\geq$ 0.75; moderate, 0.35 $<$ ES $<$ 0.75; low, ES $\leq$ 0.35; and absence of synergy, ES = 0. Positive trends were reported for synergistic combination regimens showing no significant 95% CI.

Savoldi *et al. BMC Infectious Diseases* (2021) 21:545
https://doi.org/10.1186/s12879-021-06253-x

BMC Infectious Diseases

Colistin based

RESEARCH ARTICLE Open Access

The role of combination therapy in the treatment of severe infections caused by carbapenem resistant gram-negatives: a systematic review of clinical studies

Alessia Savoldi[1*†], Elena Carrara[1†], Laura J. V. Piddock[2], Francois Franceschi[2], Sally Ellis[2], Margherita Chiamenti[1], Damiano Bragantini[1], Elda Righi[1] and Evelina Tacconelli[1,3,4]

Network meta-analysis could not be performed for any of the selected outcome given the presence of too many disconnected components

Fig. 1 Antibiotic regimens assessed in the included studies stratified by bacterial phenotype and number of patients. Legend: The antibiotics belonging to same classes are grouped. Carbapenem classes includes Group A carbapenem (doripenem, imipenem, meropenem). Tigecycline is the only agent belongs to the class of glycyclyine. Sulbactam was grouped separately for Acinetobacter. The computation of patients referred to the outcome mortality (or clinical cure, if mortality was not reported by the individual study). In case of multiple outcomes, the number of patients for each antibiotic regimen was computed for only one outcome. BLBLIs: beta lactam-beta lactam inhibitors

Savoldi et al. BMC Infectious Diseases (2021) 21:545

Colistin based – critically ill

AAC Journals.ASM.org

Polymyxin B in Combination with Antimicrobials Lacking *In Vitro* Activity versus Polymyxin B in Monotherapy in Critically Ill Patients with *Acinetobacter baumannii* or *Pseudomonas aeruginosa* Infections

Maria Helena Rigatto,[a] Fabiane J. Vieira,[b] Laura C. Antochevis,[b] Tainá F. Behle,[c] Natane T. Lopes,[d] Alexandre P. Zavascki[c,e]

Infectious Diseases Service, Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil[a]; School of Pharmaceutical Sciences, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil[b]; Infectious Diseases Service, Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil[c]; Medical School, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil[d]; Department of Internal Medicine, Medical School, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil[e]

TABLE 3 Cox proportional hazards regression model for 30-day mortality[a]

Variable	HR[b]	95% CI[c]	*P* value
Combination therapy	0.33	0.17–0.64	0.001
APACHE II score at polymyxin B initiation	1.06	1.02–1.10	0.005
Creatinine clearance of ≥60 ml/min	0.42	0.22–0.81	0.009
Polymicrobial infection	2.01	1.01–4.0	0.05

[a] Inclusion of the time to initiate therapy ($P = 0.33$) and the propensity score ($P = 0.36$) in the model did not change the results of the other variables. The propensity score for prescribing combination therapy included polymicrobial infection, *Acinetobacter baumannii* infections, connective tissue disease, and polymyxin B daily dose in a logistic regression model using a parsimonious backward stepwise method (Hosmer-Lemeshow goodness-of-fit test: $\chi^2 = 5.182$; $P = 0.64$). Body mass index, *Acinetobacter baumannii* infections, lymphoproliferative disease, Charlson score, polymyxin B dose (Table 2), and connective tissue disease (Table 1) were also evaluated in the model but did not remain because their *P* values were greater than 0.10.
[b] HR, hazard ratio.
[c] CI, confidence interval.

a retrospective analysis of a cohort study at two tertiary-care teaching hospitals in Porto Alegre, Brazil

8/101

the combination of polymyxin B with an antimicrobial lacking in vitro activity, mainly one of the carbapenems, was able to significantly and importantly decrease the risk of mortality in critically ill patients infected by XDR A. baumannii or P. aeruginosa

Antimicrob Agents Chemother 2015;59:6575–6580

International Journal of Antimicrobial Agents 35 (2010) 194–199

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

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

Short communication

Colistin therapy for microbiologically documented multidrug-resistant Gram-negative bacterial infections: a retrospective cohort study of 258 patients

Matthew E. Falagas[a,b,c,*], Petros I. Rafailidis[a,b], Elda Ioannidou[a], Vangelis G. Alexiou[a], Dimitrios K. Matthaiou[a], Drosos E. Karageorgopoulos[a], Anastasios Kapaskelis[a,b], Dimitra Nikita[d], Argyris Michalopoulos[a,e]

[a] Alfa Institute of Biomedical Sciences (AIBS), 9 Neapoleos Street, 15 123 Marousi, Athens, Greece
[b] Department of Medicine, Henry Dunant Hospital, Athens, Greece
[c] Department of Medicine, Tufts University School of Medicine, Boston, MA, USA
[d] Department of Microbiology, Henry Dunant Hospital, Athens, Greece
[e] Department of Critical Care, Henry Dunant Hospital, Athens, Greece

Colistin based

October 2000 to May 2005, retrospective cohort study, Greece

Table 2
Outcome of infection due to different pathogens, according to the specific therapeutic regimen received.

Pathogen	Infection outcome	Regimen					
		COL monotherapy[a]	COL + MER[b]	COL + PIP/TAZ	COL + SAM	COL + other agents[c]	All regimens
Acinetobacter baumannii	Cure [*n*/*N* (%)]	20/23 (87.0)*	99/118 (83.9)†	4/6 (67.7)	8/11 (72.7)	7/12 (58.3)	138/170 (81.2)
	Deterioration [*n*/*N* (%)]	3/23 (13.0)*	19/118 (16.1)†	2/6 (33.3)	3/11 (27.3)	5/12 (41.7)	32/170 (18.8)
Pseudomonas aeruginosa	Cure [*n*/*N* (%)]	9/12 (75.0)	24/28 (85.7)	6/10 (60)	1/1	11/17 (64.7)	51/68 (75.0)
	Deterioration [*n*/*N* (%)]	3/12 (25.0)	4/28 (14.3)	4/10 (40)	0/1	6/17 (25.3)	17/68 (25.0)
Klebsiella pneumoniae	Cure [*n*/*N* (%)]	0	11/15 (73.3)	1/1	–	1/2	15/18 (83.3)
	Deterioration [*n*/*N* (%)]	0	4/15 (26.7)	0/1	–	1/2	5/18 (27.8)
All pathogens	Cure [*n*/*N* (%)]	30/36 (83.3)**	135/162 (83.3)††	11/17 (64.7)	9/12 (75.0)	19/31 (61.3)	204/258 (79.1)
	Deterioration [*n*/*N* (%)]	6/36 (16.7)**	27/162 (16.7)††	6/17 (35.3)	3/12 (25.0)	12/31 (38.7)	54/258 (20.9)

COL, colistin; MER, meropenem; PIP/TAZ, piperacillin/tazobactam; SAM, ampicillin/sulbactam.
Relative comparisons for infections caused by *P. aeruginosa* and *K. pneumoniae* were not meaningful because of the small number of cases.

[a] Statistically significant differences between groups of patients—COL monotherapy vs. COL + PIP/TAZ or COL + SAM or COL + other agents: *$P = 0.076$ (not significant) for infections caused by *A. baumannii*; **$P = 0.05$ for infections caused by all pathogens.

[b] Statistically significant differences between groups of patients—COL + MER vs. COL + PIP/TAZ or COL + SAM or COL + other agents: †$P = 0.026$ for infections caused by *A. baumannii*; ††$P = 0.003$ for infections caused by all pathogens.

[c] Other agents included aminoglycosides (11 patients), imipenem (10 patients), cephalosporins (7 patients), aztreonam (2 patients) and ciprofloxacin (1 patient).

International Journal of Antimicrobial Agents 35 (2010) 194-199

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial

Mical Paul, George L Daikos, Emanuele Durante-Mangoni, Dafna Yahav, Yehuda Carmeli, Yael Dishon Benattar, Anna Skiada, Roberto Andini, Noa Eliakim-Raz, Amir Nutman, Oren Zusman, Anastasia Antoniadou, Pia Clara Pafundi, Amos Adler, Yaakov Dickstein, Ioannis Pavleas, Rosa Zampino, Vered Daitch, Roni Bitterman, Hiba Zayyad, Fidi Koppel, Inbar Levi, Tanya Babich, Lena E Friberg, Johan W Mouton, Ursula Theuretzbacher, Leonard Leibovici

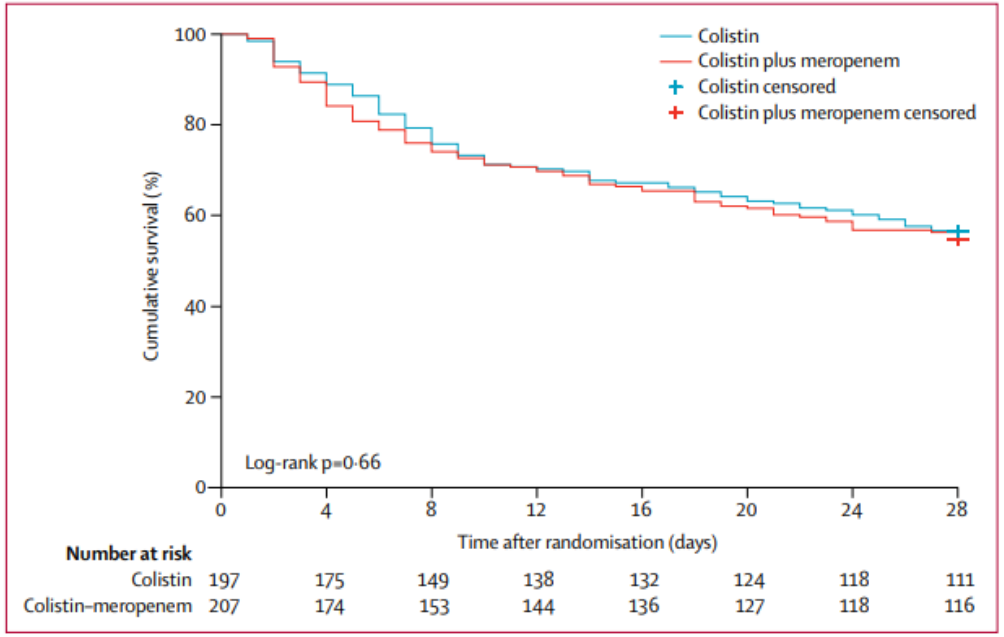

Figure 2: **Survival analysis to day 28 after randomisation**

	Colistin	Colistin and meropenem	Risk ratio (95% CI) for outcome with combination	p value
Per protocol population*				
n	169	185	..	..
Clinical failure	129 (76%)	131 (71%)	0·92 (0·82–1·05)	0·220
28-day mortality	69 (41%)	75 (41%)	0·97 (0·76–1·25)	0·840
14-day mortality	48 (28%)	53 (29%)	1·00 (0·72–1·39)	0·992
Inappropriate empirical antibiotic treatment†				
n	92	105	..	..
Clinical failure	74 (80%)	76 (72%)	0·91 (0·78–1·07)	0·254
28-day mortality	40 (43%)	44 (42%)	0·98 (0·71–1·36)	0·910
14-day mortality	34 (37%)	28 (27%)	0·74 (0·49–1·13)	0·166
Bloodstream infection, ventilator-associated pneumonia, or hospital-acquired pneumonia				
n	173	182	..	..
Clinical failure	141 (82%)	133 (73%)	0·9 (0·8–1·004)	0·059
28-day mortality	77 (45%)	81 (45%)	0·99 (0·79–1·25)	0·931
14-day mortality	55 (328%)	60 (33%)	1·04 (0·78–1·38)	0·804
Main pathogen				
n	198	208	..	..
Clinical failure				
Acinetobacter baumannii	125 (83%), n=151	130 (81%), n=161	0·97 (0·87–1·09)	0·643
Enterobacteriaceae‡	23 (68%), n=34	18 (46%), n=39	0·78 (0·54–1·13)	0·185
Pseudomonas or others§	8 (62%), n=13	4 (50%), n=8	0·81 (0·36–1·84)	0·673
28-day mortality				
A baumannii	70 (46%), n=151	84 (52%), n=161	1·11 (0·87–1·41)	0·404
Enterobacteriaceae	12 (35%), n=34	8 (21%), n=39	0·62 (0·29–1·36)	0·235
Pseudomonas or others	4 (31), n=13	2 (25%), n=8	0·81 (0·19–3·47)	1·0
14-day mortality				
A baumannii	54 (36%), n=151	62 (39%), n=161	1·11 (0·82–1·52)	0·495
Enterobacteriaceae	6 (18%), n=34	6 (15%), n=39	0·90 (0·32–2·51)	0·838
Pseudomonas or others	4 (31%), n=13	2 (25%), n=8	0·81 (0·19–3·47)	1·0

n values indicated for outcomes assessed in a specific patient subgroup. *Surviving 48 h and no modification in the first 5 days after randomisation. †No covering treatment until day 3 after culture taken. Appropriate empirical antibiotic treatment consisted of colistin in all but nine patients who received aminoglycosides (three patients), co-trimoxazole, tigecycline, ampicillin–sulbactam, minocycline, gentamicin plus chloramphenicol and gentamicin plus tigecycline (one patient each). ‡Includes polymicrobial infections in which at least one of the carbapenem-resistant Gram-negative bacteria were Enterobacteriaceae; 66 of 72 patients had *Klebsiella pneumoniae* infections. §Includes *Pseudomonas aeruginosa* and *A baumannii* polymicrobial infections; 19 of 21 patients had *P aeruginosa* infections. Unstratified analysis due to small numbers.

Table 4: **Subgroup analyses**

Colistin based

A randomised controlled superiority trial
six hospitals in Israel, Greece, and Italy
Oct 1, 2013, and Dec 31, 2016

Lancet Infect Dis 2018; 18: 391–400

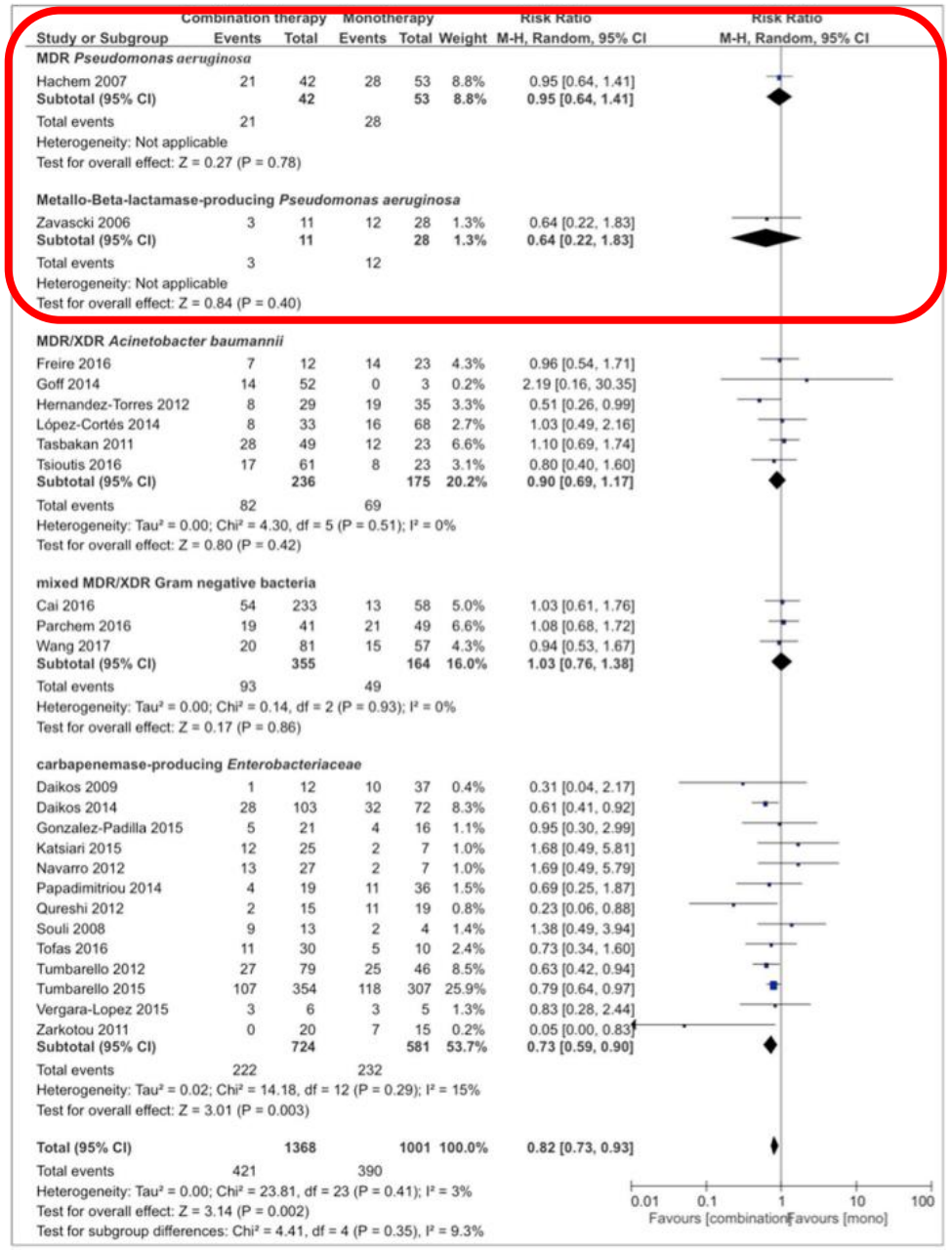

Figure 3. Risk ratios for mortality rates of case series and cohort studies stratified by different bacteria. Combination therapy with at least two *in vitro* active substances. Data markers indicate RRs and error bars indicate 95% CIs.

www.nature.com/scientificreports

SCIENTIFIC REPORTS
nature research

Colistin based

OPEN

Monotherapy versus combination therapy for multidrug-resistant Gram-negative infections: Systematic Review and Meta-Analysis

Adrian Schmid, Aline Wolfensberger, Johannes Nemeth, Peter W. Schreiber, Hugo Sax & Stefan P. Kuster*

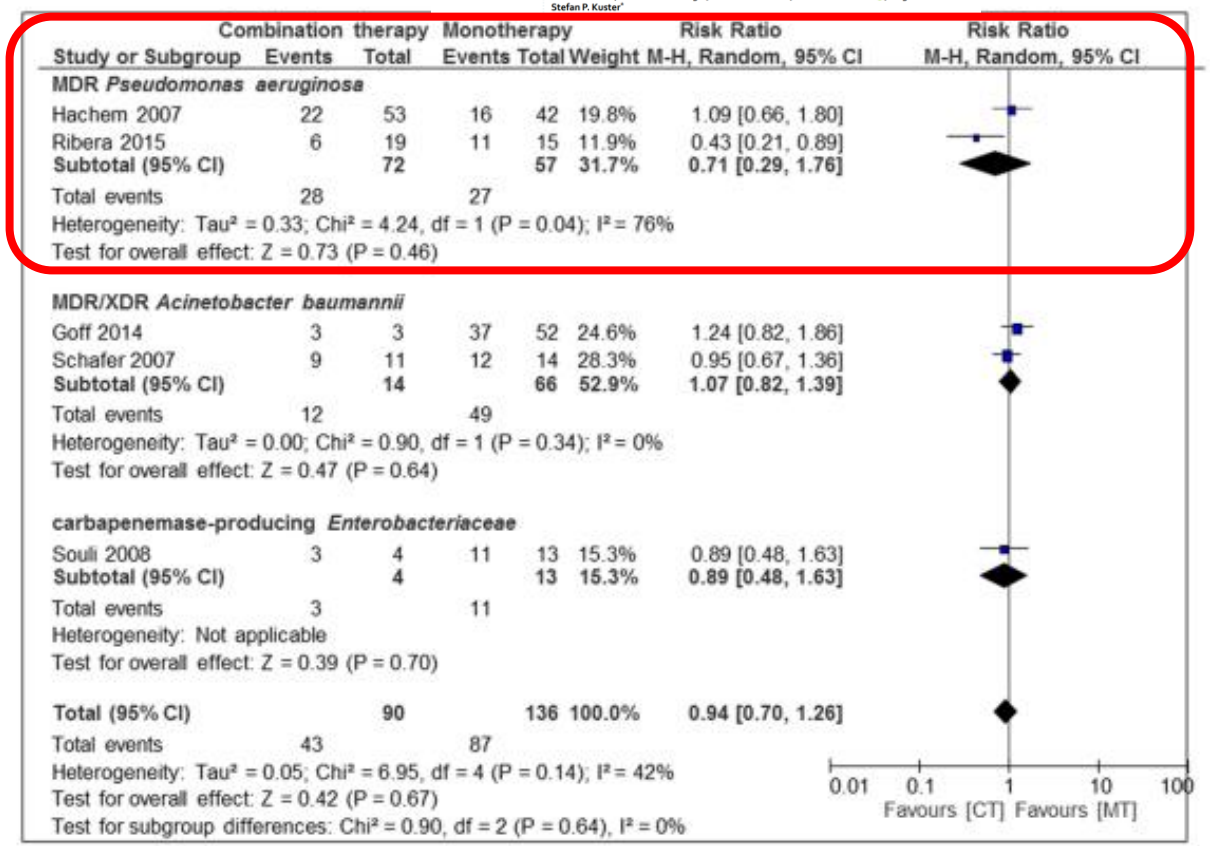

Figure 5. Risk ratios for clinical cure rates of case series and cohort studies stratified by different bacteria. Combination therapy with at least two *in vitro* active substances. Data markers indicate Risk ratios and error bars indicate 95% CIs.

Scientific Reports (2019) 9:15290

XVII. Should Monotherapy or Combination Therapy Be Used to Treat Patients With HAP/VAP Due to *P. aeruginosa*?

Recommendations

1. For patients with HAP/VAP due to *P. aeruginosa* who are not in septic shock or at a high risk for death, and for whom the results of antibiotic susceptibility testing are known, we recommend monotherapy using an antibiotic to which the isolate is susceptible rather than combination therapy *(strong recommendation, low-quality evidence)*.
2. For patients with HAP/VAP due to *P. aeruginosa* who remain in septic shock or at a high risk for death when the results of antibiotic susceptibility testing are known, we suggest combination therapy using 2 antibiotics to which the isolate is susceptible rather than monotherapy *(weak recommendation, very low-quality evidence)*.
3. For patients with HAP/VAP due to *P. aeruginosa*, we recommend against aminoglycoside monotherapy *(strong recommendation, very low-quality evidence)*.

   Remarks: High risk of death in the meta-regression analysis was defined as mortality risk >25%; low risk of death is defined as mortality risk <15%. For a patient whose septic shock resolves when antimicrobial sensitivities are known, continued combination therapy is not recommended.

Management of Adults With HAP/VAP; ATS/IDSA guideline 2016

Novel beta lactam

Novel beta lactams

Although a newer b-lactam may be considered for empiric treatment of MDR-PSA in some cases, these agents remain largely omitted from treatment guidelines.

Drugs (2021) 81:2117–2131

Table 1 Initial treatment of *Pseudomonas aeruginosa* pneumonia[a]

One of the following	
Ceftazidime	IV 2 g Q8–12 h
Cefepime	IV 1–2 g Q8 h
Piperacillin-tazobactam	IV 4.5 g Q6 h
Meropenem	IV 2 g Q8 h
Imipenem	IV 500 mg Q6 h or 1 g Q8 h
Aztreonam[b]	IV 2 g every 8 h
Plus one of the following if treating with combination therapy	
Tobramycin	IV 7 mg/kg od[c]
Gentamicin	IV 7 mg/kg od[c]
Levofloxacin	IV or PO 750 mg od
Ciprofloxacin	IV or PO 400 mg od
Amikacin	IV 20 mg/kg od[d]
Antimicrobial options for MDR-*P. aeruginosa* pneumonia	
Ceftolozane-tazobactam	IV 3 g Q8 h
Ceftazidime-avibactam	IV 2.5 g Q8 h
Imipenem-cilastatin-relebactam	IV 1.25 g Q6 h
Cefiderocol	IV 2 g Q6–8 h

IV intravenous, *MDR* multi-drug resistant, *od* once daily, *PO* oral, *Q* every

[a]Dosages recommended based on normal renal and hepatic function

[b]Typically reserved for patients with beta-lactam allergy

[c]Dose should be adjusted for serum trough concentration < 1 µg/mL

[d]Dose should be adjusted for serum trough concentration < 5 µg/mL

Clinical Infectious Diseases

MAJOR ARTICLE

Novel beta lactam

Ceftolozane/Tazobactam vs Polymyxin or Aminoglycoside-based Regimens for the Treatment of Drug-resistant *Pseudomonas aeruginosa*

Jason M. Pogue,[1] Keith S. Kaye,[2] Michael P. Veve,[3] Twisha S. Patel,[4] Anthony T. Gerlach,[5] Susan L. Davis,[6] Laura A Puzniak,[7] Tom M. File,[8] Shannon Olson,[9] Sorabh Dhar,[10] Robert A. Bonomo,[11] and Federico Perez[11]

[1]Department of Clinical Pharmacy, University of Michigan College of Pharmacy, and [2]Division of Infectious Diseases, University of Michigan Medical School, Ann Arbor, Michigan; [3]Department of Clinical Pharmacy and Translational Science, University of Tennessee College of Pharmacy, Nashville, Tennessee; [4]Department of Pharmacy Services, Michigan Medicine, Ann Arbor, Michigan; [5]Department of Pharmacy Services, the Ohio State University Wexner Medical Center, Columbus, Ohio; [6]Department of Pharmacy, Henry Ford Hospital, Ann Arbor, Michigan; College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan; [7]Merck & Co, Inc, Kenilworth, New Jersey; [8]Division of Infectious Diseases Summa Health, Northeast Ohio Medical University, Rootstown, Ohio; [9]Department of Pharmacy, Sinai Grace Hospital; Detroit Medical Center, Detroit, Michigan and [10]Department of Internal Medicine, Detroit Medical Center, Wayne State University School of Medicine, Michigan; and [11]Division of Infectious Diseases and HIV Medicine, Louis Stokes Cleveland VA Medical Center, Case Western Reserve University School of Medicine, Cleveland, Ohio

Retrospective, observational cohort study performed at 6 centers in USA from 1 January 2010 through 30 May 2018

Table 3. Comparative clinical outcomes between Ceftolozane/Tazobactam and Polymyxin or Aminoglycoside treated patients

Outcome	Ceftolozane/ Tazobactam (N = 100)	Polymyxin/Aminoglycoside (N = 100)	*P* Value	Odds Ratio (95% CI)	Adjusted Odds Ratio[a] (95% CI)
Clinical cure	81	61	.002	2.72 (1.43–5.17)	2.63 (1.31–5.30)
In-hospital mortality	20	25	.40	0.75 (0.38–1.46)	0.62 (.30–1.28)
Acute kidney injury	6	34	<.001	0.12 (0.05–0.31)	0.08 (.03–.22)

Clinical Infectious Diseases 2020;71(2):304–10

Table 2. Infection and Treatment-related Characteristics

Covariate	Ceftolozane/ Tazobactam (N = 100)	Polymyxin/ Aminoglycoside (N = 100)	*P* Value
Severity of illness and infection-related variables			
Intensive care unit at infection onset	70	68	.76
No sepsis	14	11	.67
Sepsis	48	43	.57
Severe sepsis	15	23	.21
Septic shock	23	23	1.00
Severe sepsis or septic shock	38	46	.22
Vasopressors during therapy	30	34	.54
SOFA (sequential organ failure assessment) score[a]	8 (6–10) (n = 54)[b]	8 (5–10) (n = 63)[b]	.48
Polymicrobial infection	40	46	.39
Site of infection			
Ventilator-associated pneumonia	52	51	1
Hospital-acquired pneumonia	12	24	.04
Urinary tract	16	11	.41
Wound	13	8	.36
Other	7	6	
Presence of bacteremia	6	8	.58
Treatment-related variables			
Infectious diseases consult	100	92	.004
Time to active therapy (hours)[a]	55.5 (23–80.25)	43.5 (4.2–72.3)	.10
Time to study drug (hours)[a]	63.5 (45.3–92)	53.3 (5–93)	.08
Combination therapy	15	72	<.001
Aminoglycoside	0	2	
Polymyxin	0	2	
Ciprofloxacin	3	6	
Meropenem	0	36	
Cefepime	0	8	
Ceftazidime	0	2	
Piperacillin/Tazobactam	0	9	
Aztreonam	0	2	
Inhaled colistin	9	1	
Inhaled aminoglycoside	3	4	
In vitro activity of combination agent			
Susceptible	15	24	
Intermediate	0	17	
Resistant	0	31	
Duration of therapy (days)[a]	9.5 (7–14)	9 (6–14)	.17

[a]Median (interquartile range), otherwise data are presented as n (and percent as n = 100).
[b]Number of patients where all variables were available to calculate SOFA score.

Clinical Infectious Diseases

IDSA FEATURES

Infectious Diseases Society of America Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] and Cornelius J. Clancy[6]

[1]Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, [2]Division of Pharmacy, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, [3]Medical Service, Louis Stokes Cleveland Department of Veterans Affairs Medical Center, University Hospitals Cleveland Medical Center and Departments of Medicine, Pharmacology, Molecular Biology, and Microbiology, Case Western Reserve University, Cleveland, Ohio, USA, [4]Departments of Medicine and Pathology, University of Virginia, Charlottesville, Virginia, USA, [5]Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, North Carolina, USA, and [6]Department of Medicine, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Question 3: 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 the preferred treatment options for the treatment of infections outside of the urinary tract caused by DTR-*P. aeruginosa*.

Question 4: 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 (ie, ceftolozane-tazobactam, ceftazidime-avibactam, or imipenem-cilastatin-relebactam) has been confirmed.

cid 2021:72 (1 April)

Guidelines

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine)

Mical Paul [1, 2, §], Elena Carrara [3, §], Pilar Retamar [4, 5], Thomas Tängdén [6], Roni Bitterman [1, 2], Robert A. Bonomo [7, 8, 9], Jan de Waele [10], George L. Daikos [11], Murat Akova [12], Stephan Harbarth [13], Celine Pulcini [14, 15], José Garnacho-Montero [16], Katja Seme [17], Mario Tumbarello [18], Paul Christoffer Lindemann [19], Sumanth Gandra [20], Yunsong Yu [21, 22, 23], Matteo Bassetti [24, 25] … Jesús Rodríguez-Baño [4, 5, §]

3. Carbapenem-resistant *Pseudomonas aeruginosa*

Question 3.1: What is the antibiotic of choice for CRPA

Recommendations

- In patients with severe infections due to DTR-CRPA, we suggest therapy with ceftolozane-tazobactam if active *in vitro* (**conditional recommendation for use, very low certainty of evidence**). Insufficient evidence is available for imipenem-relebactam, cefiderocol and ceftazidime-avibactam at this time.
- In patients with non-severe or low-risk CRPA infections under the consideration of antibiotic stewardship, we consider it good clinical practice to use the old antibiotics, chosen from among the *in vitro* active antibiotics on an individual basis and according to the source of infection (**good practice statement**).

Question 3.2: Should combination therapy be used for the treatment of CRPA?

Recommendations

- Lacking evidence, we cannot recommend for or against the use of combination therapy with the new BLBLI (ceftazidime-avibactam and ceftolozane-tazobactam) or cefiderocol for CRPA infections.
- When treating severe infections caused by CRPA with polymyxins, aminoglycosides, or fosfomycin, we suggest treatment with two *in vitro* active drugs (**conditional recommendation for use, very low certainty of evidence**). No recommendation for or against specific combinations can be provided.
- In patients with non-severe infections or low-risk CRPA infections, under the consideration of antibiotic stewardship, we consider it good clinical practice to use monotherapy chosen from among the drugs active *in vitro*, on an individual basis and according to the source of infection (**good practice statement**).

Review of the evidence

Similar to the choice of monotherapy, there is a paucity of data on combination therapy for DTR-CRPA.

Clinical microbiology and infection 28 (2022) 521-547

Summary

- Pseudomonas 15-20%, Resistance increasing (MDR up to 40%)
- DST based definite therapy
  - Remain septic shock or high risk for death – double (when emergent resistance is high and bacteremia in high risk)
  - Without risk – single
    - Non MDR: based on DST
      - Aminoglycoside mono x
      - No need to choose carbapenem if other b-lactam is possible
    - MDR: based on DST
      - Colistin (combination in severe case?), ceftolozane/tazobactam?

Key Question

For patients with pseudomonas infection after confirming the culture result, should be considered for combination antibiotics?

→There is no definite evidence to choose a combination therapy in non severe non MDR pseudomonas pneumonia

→New beta lactam may decrease the practical use of colistin based combination therapy for MDR pseudomonas pneumonia

감사합니다.