SCUOLA DI SPECIALIZZAZIONE IN MALATTIE INFETTIVE E TROPICALI

PANDORA ID - 24

TIME TO WEBINAR IN INFECTIOUS DISEASES

PROGETTO DI FORMAZIONE

Anno Accademico 23/24

LA TERAPIA DI COMBINAZIONE ANTIBATTERICA: PRO E CONTRO

22 Aprile 2024 – Ore 16.00-19.00

16.00-19.00	**LA TERAPIA DI COMBINAZIONE ANTIBATTERICA: PRO E CONTRO** Moderatore: Prof.ssa Alessandra Bandera (Milano)
16.00	**Il paziente critico** Bruno Viaggi (Firenze)
16.20	**Discussione**
16.30	**Le infezioni Enterobacterales MDR** Elena Carrara (Verona)
16.50	**Discussione**
17.00	**Le infezioni da *Pseudomonas aeruginosa*** Daniele Roberto Giacobbe (Genova)
17.20	**Discussione**
17.30	**L'infezione complicata da *Staphylococcus aureus*** Michele Bartoletti (Milano)
17.50	**Discussione**
18.00	**Review di Casistica Clinica** (2 interventi di Specializzandi 15' max + 5' discussione)
18.45	**Conclusioni e chiusura dei lavori**

La terapia di Combinazione Antibatterica: Pro e Contro - il *paziente critico*

Bruno Viaggi

Unit Infezioni Correlate all'assistenza del Paziente Critico
Dipartimento di Anestesia NeuroRianimazione AOU Careggi

Gruppo Tecnico Programma Lotta alla Sepsi
Coordinamento e Gruppo Tecnico AID
REGIONE TOSCANA

Dichiarazione su potenziali conflitti di interesse

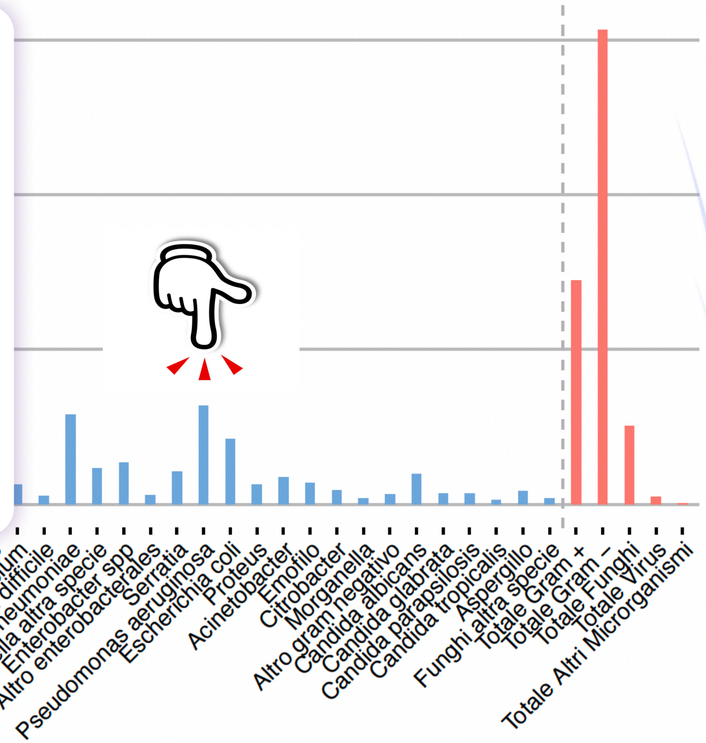
Consulenze, partecipazione advisory boards, speaker's bureau, contratti/contributi di ricerca e di eventi studio:

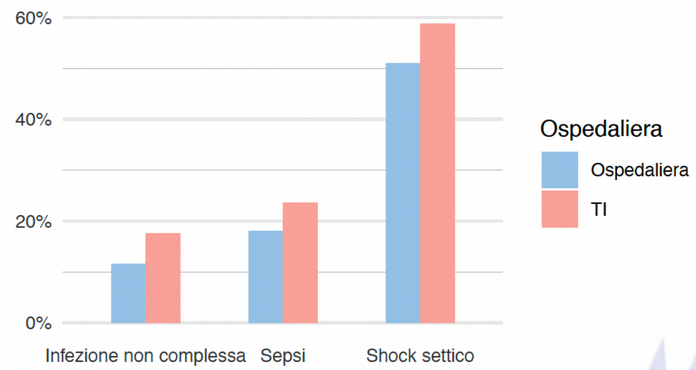
Abbott, Accelerate Diagnostics, Ada, Advanz Pharma, Alifax, Angelini, Becton Dickinson, Bellco, Biomerieux, Biotest, Cepheid, Correvio, Diasorin, Emmegi Diagnostica, Gilead, InfectoPharm, Menarini, MSD Italia, Nordic Pharma, Pfizer, Shionogi, Thermofischer Scientific, Viatris

Petalo Infectionlight - GiViTi - Anno 2023

Enterobacterales percentuale di Resistenza

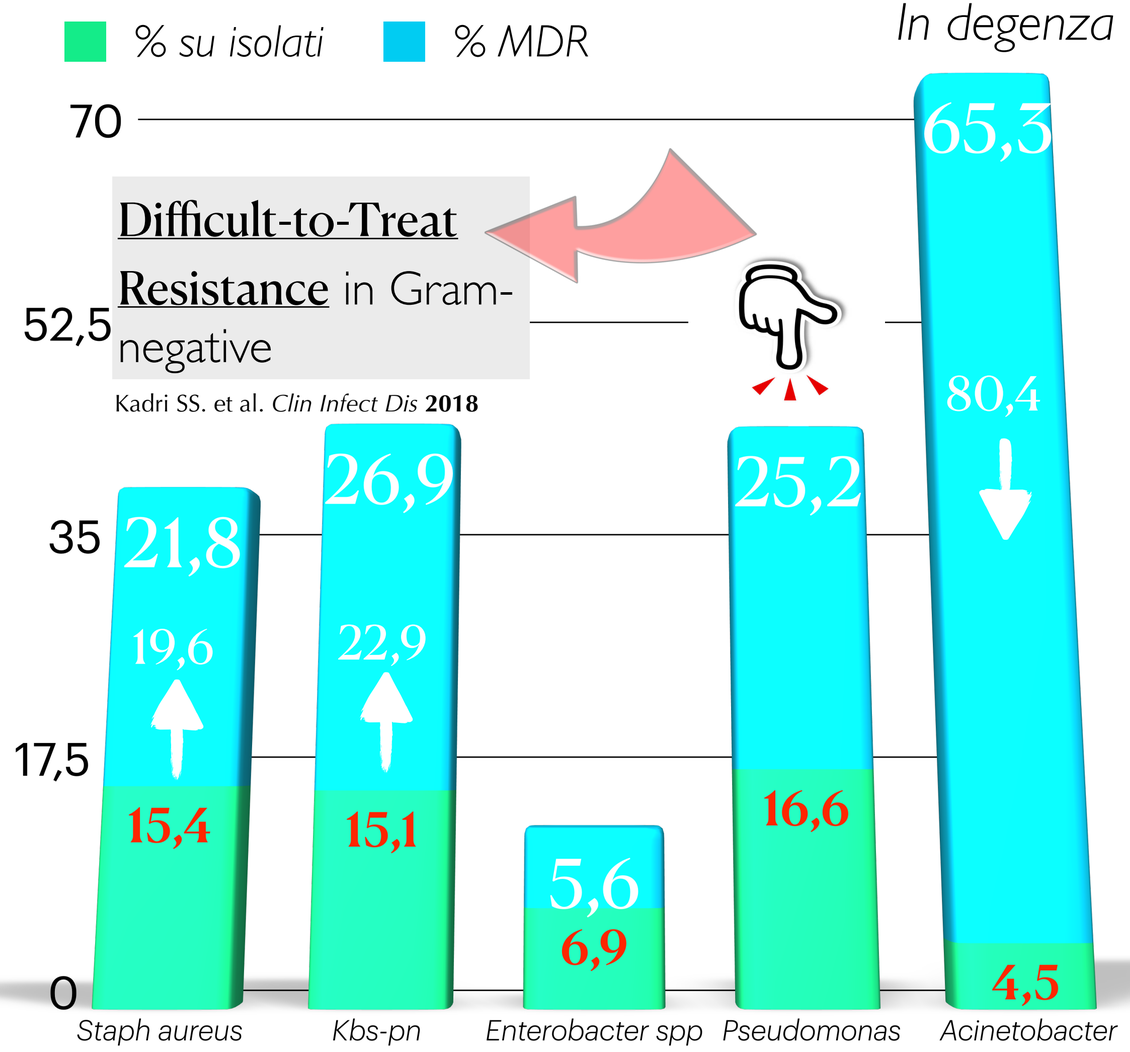
	% R
IMP	3,1
KPC	55,0
NDM	19,1
OXA	13,0
VIM	9,9





Mortalità per gravità infezione (%)	TI	Ospedaliera
Infezione non complessa	11.6	17.5
Sepsi	18.0	23.6
Shock settico	50.9	58.8

In degenza



LESS IS MORE IN INTENSIVE CARE

Less is more: critically ill status is not a carte blanche for unlimited antibiotic use

Andre C. Kalil[1*] and Jean-Francois Timsit[2,3] *Intensive Care Med* **2020**

The single most important risk factor for the development of antibiotic resistance is the overuse of antibiotics in both humans and animals

Standard patient protection by the infection control program
Compliance with hand hygiene
Control of transmission of multi-drug-resistant bacteria
*1. **Collect** microbiological samples before starting antimicrobial therapy, given individual patient's clinical presentation*
*2. **Use** proven effective short-course antibiotic regimens:*
*(a) Hospital-acquired and ventilator-associated pneumonia: **7 days***
*(b) Community-acquired pneumonia: **5 days***
*(c) Acute exacerbation of chronic bronchitis: **3 days***
*(d) Complicated intra-abdominal infections: **4 days***
*(e) Complicated urinary tract infection: **5 days***
*3. **Do not start** broad-spectrum antibiotics for the outdated HCAP definition. Instead, use the MDR risk factors from the HAP/VAP and CAP*
*4. **Do not administer** antibiotics for VAT without indication of pneumonia*
*5. **DO NOT USE** combination antibiotic therapy for known susceptible bacterial infections*
*6. **Address** source control as rapidly as possible (e.g., catheter removal, abscess drainage)*
*7. **Optimize** antibiotic pharmacokinetics and pharmacodynamics (PK/PD) parameters*
*8. **De-escalate** antibiotics when patient is showing clinical improvement and/or cultures are negative*

Shorter is better

The film "Blade Runner 2049" depicts a bleak view of humanity 30 years from now, ***a world in which survival will be much more difficult than today***. You may say we are lucky that it is only 2020; ***however, we are already facing a growing and unstoppable shortage of antibiotics worldwide due to bacterial resistance***, and this could end up in a humanitarian disaster

*Our 2020 bedside actions to prevent antibiotic overuse **can curtail the development of antibiotic resistance** and beat the Blade Runner's gloomy prediction for 2049*

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7. Optimize antibiotic pharmacokinetics and pharmacodynamics (PK/PD) parameters
8. De-escalate antibiotics when patient is showing clinical improvement and/or cultures are negative

Recommendations

19. For adults with sepsis or septic shock and high risk for multidrug resistant (MDR) organisms, we **suggest** using two antimicrobials with gram-negative coverage for empiric treatment over one gram-negative agent

Weak recommendation, very low quality of evidence

20. For adults with sepsis or septic shock and low risk for MDR organisms, we **suggest against** using two Gram-negative agents for empiric treatment, as compared to one Gram-negative agent

Weak recommendation, very low quality of evidence

21. For adults with sepsis or septic shock, we **suggest against** using double gram-negative coverage once the causative pathogen and the susceptibilities are known

Weak recommendation, very low quality of evidence

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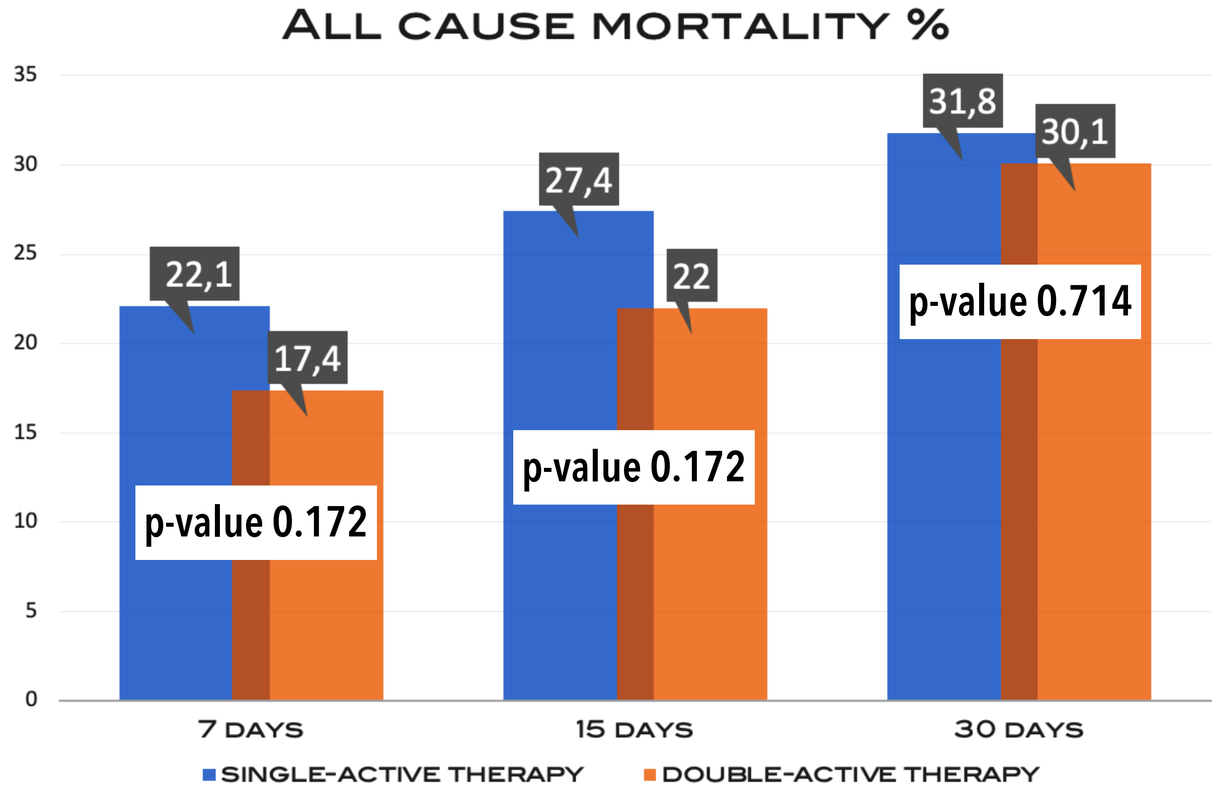
Influence of empirical ***double-active combination*** antimicrobial therapy compared with active monotherapy on mortality in patients with septic shock: a propensity score-adjusted and matched analysis

Ripa M. et al. *J Antimicrob Chemother* **2017**; **72**:3443-3452

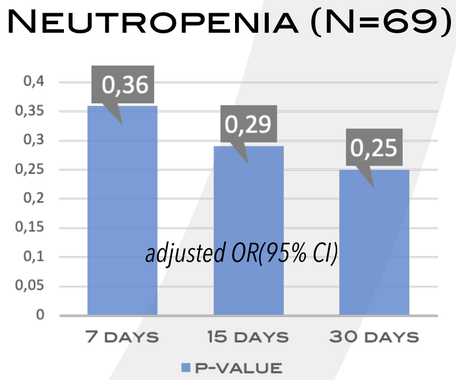
576 patients with monomicrobial septic shock who received active empirical antimicrobial therapy were included

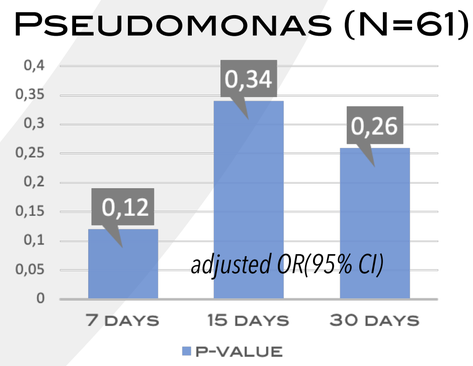
340 received AM and ***236*** DACT

DACT *double-active combination antimicrobial therapy* ***AM*** *active monotherapy*



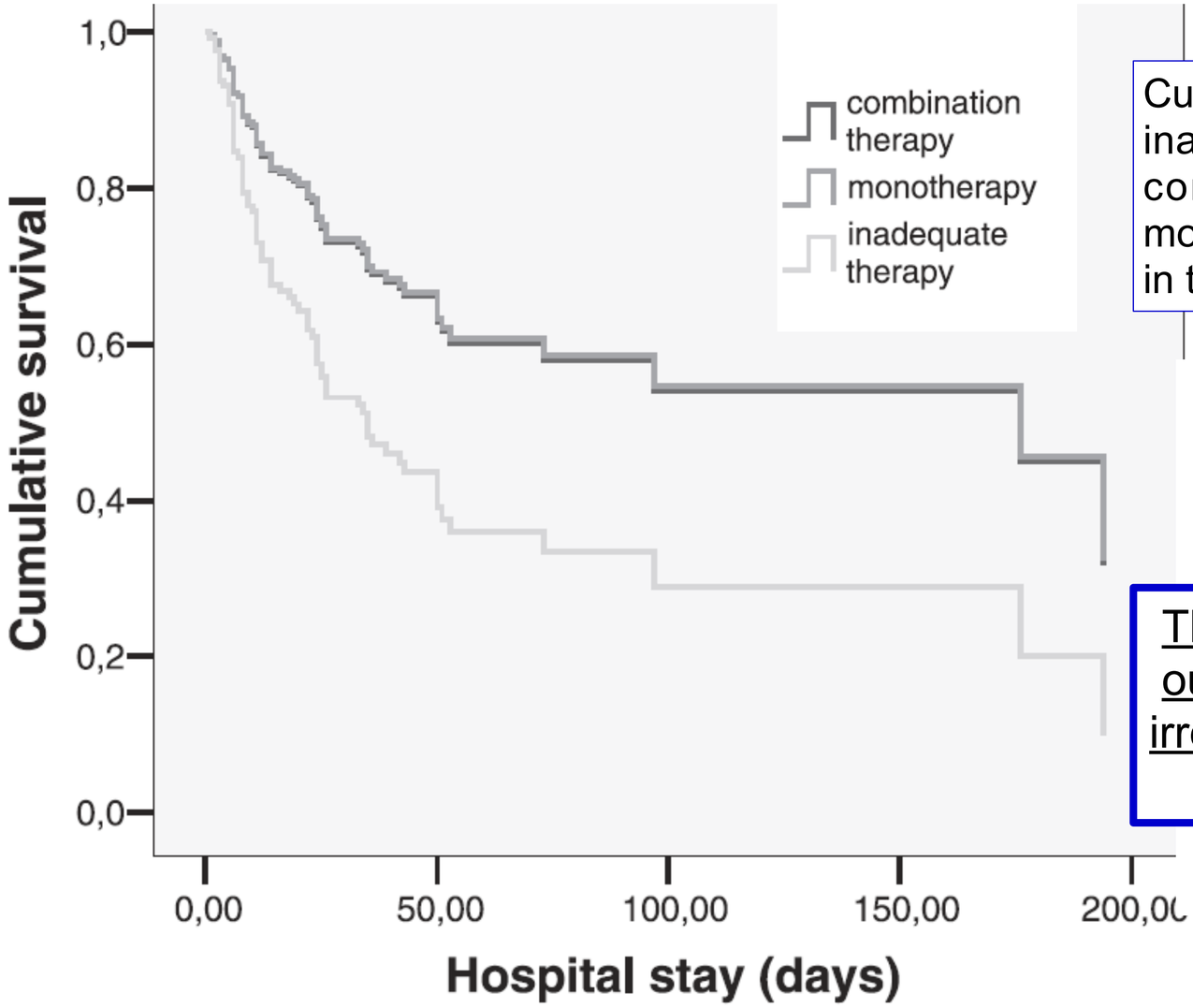
No difference in 7, 15 and 30 day all-cause mortality was found





Optimal management therapy for *Pseudomonas aeruginosa* ***VAP***: An observational, multicenter study comparing ***monotherapy*** with ***combination*** antibiotic therapy

Garnacho-Montero J. et al. *Crit Care Med* **2007**; 35:1888–1895



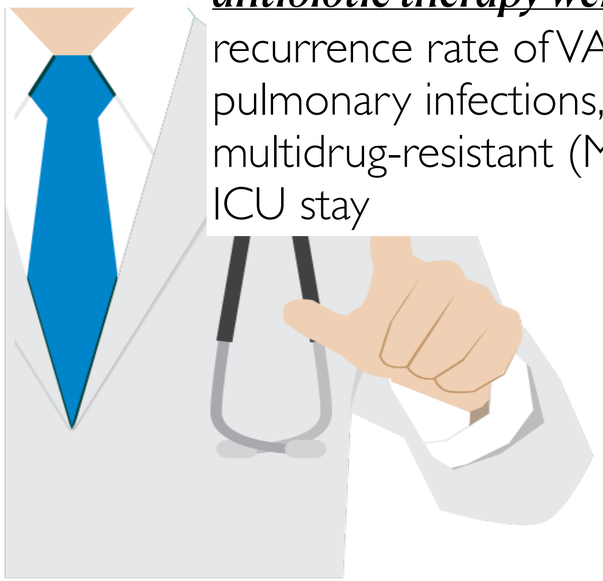
Cumulative survival curves of patients with inappropriate empirical antibiotic therapy compared with patients with effective monotherapy or effective combined therapy in the empirical therapy

The variable associated with favorable outcome is the adequacy of treatment, irrespective of the combo or non combo regimen

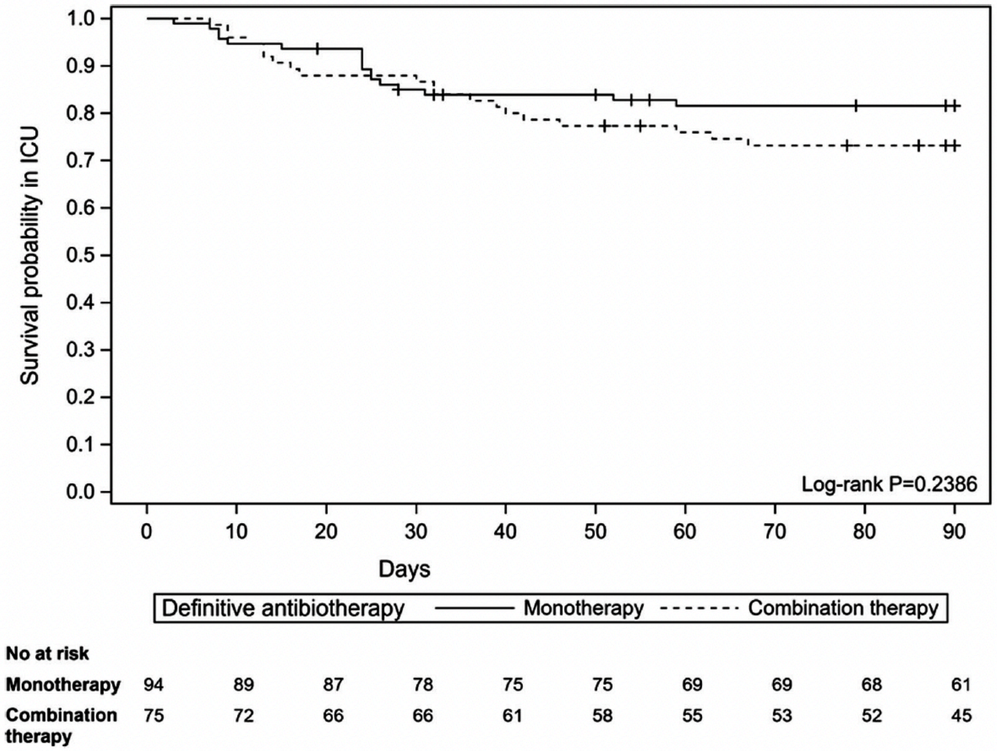
Association between combination antibiotic therapy as opposed as monotherapy and outcomes of ICU patients with *Pseudomonas aeruginosa* ventilator-associated pneumonia: an ancillary study of the ***iDIAPASON*** trial

Foucrier A. et al. *Crit Care* **2023**; 27:211

RESULTS: at day 90, among ***37*** patients (21.9%) who died, ***17*** received monotherapy and ***20*** received a combination therapy (P = 0.180). ***Monotherapy and combination antibiotic therapy were similar for*** the recurrence rate of VAP, the number of extra pulmonary infections, or the acquisition of multidrug-resistant (MDR) bacteria during the ICU stay



	Monotherapy *N* = 94	Combination therapy *N* = 75	*P*-value
ICU mortality	17 (18.1)	20 (26.7)	0.1801
Recurrence of VAP	15 (16.0)	8 (10.7)	0.3190
Number of days under mechanical ventilation[a]	23.0 [12.0; 34.0]	28.0 [16.5; 50.0]	0.0243
Length of stay in intensive care unit (days)	33.0 [21.0; 51.0]	38.0 [25.0; 60.0]	0.0654
Number of extra pulmonary infections during ICU stay[b]	1.0 [0.0; 2.0]	0.0 [0.0; 2.0]	0.8971
MDR pathogens acquired during ICU stay[c]	18 (19.8)	16 (21.9)	0.7372



No at risk										
Monotherapy	94	89	87	78	75	75	69	69	68	61
Combination therapy	75	72	66	66	61	58	55	53	52	45

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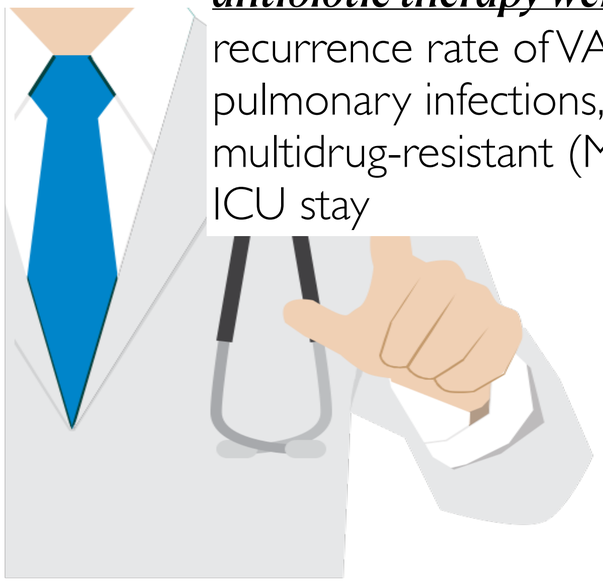
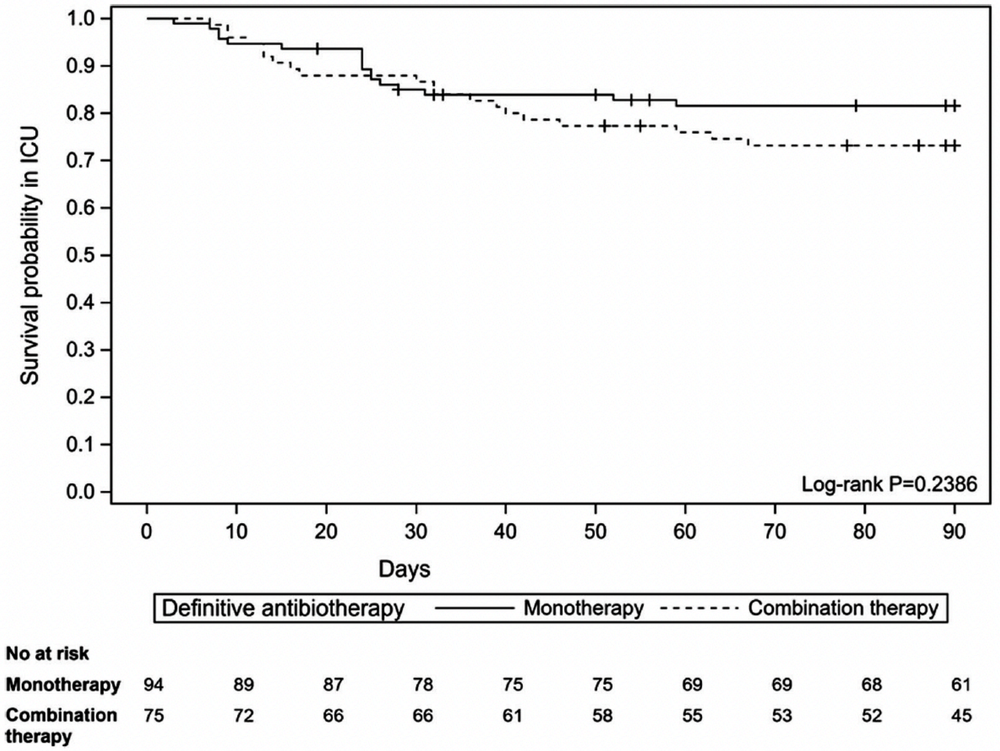


CONCLUSION

the use of combination therapy versus monotherapy ***was not associated*** with a difference in mortality or PA-VAP recurrence in ICU at day 90



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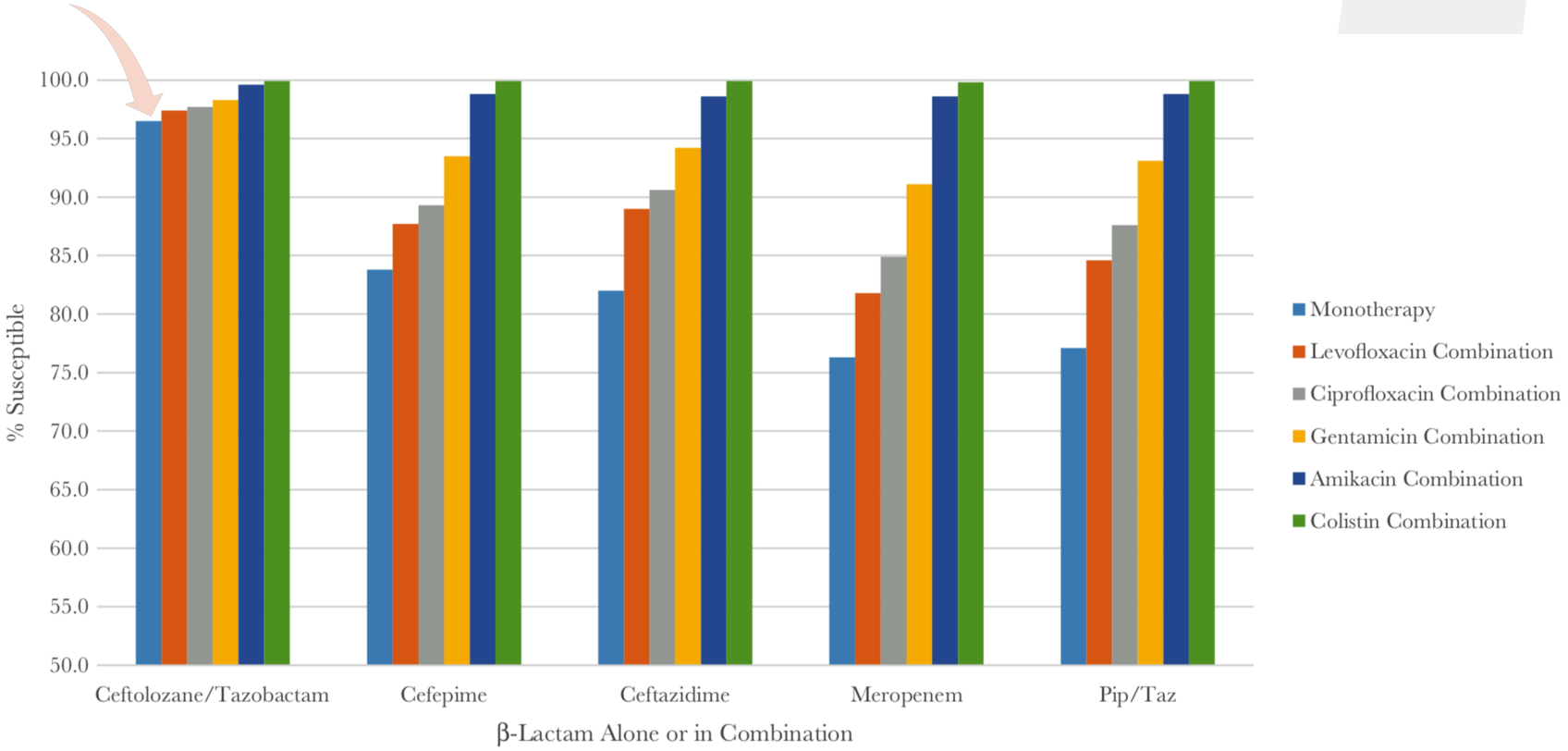
Comparison of the in Vitro ***Susceptibility*** of ***C/T*** with the Cumulative susceptibility Rates of Standard Antibiotic combinations when tested against *Pseudomonas aeruginosa* from ICU patients with BSIs or Pneumonia

Shortridge D. et al. *Open Forum Infect Dis* **2019**

Methods: Isolates were collected from intensive care unit patients hospitalized in 32 US hospitals from 2011 to 2017. The susceptibilities of 1543 *P. aeruginosa* isolates from bloodstream infections (198 isolates, 12.8%) or pneumonia (1345 isolates, 87.2%) were determined for ceftolozane-tazobactam and comparators



A threshold of 95% susceptibility was used for comparison as recommended in the IDSA guidelines for management of patients with HAP/VAP

Novel BLICs as monotherapy versus combination for the treatment of drug-resistant *Pseudomonas aeruginosa* infections: A multicenter cohort study

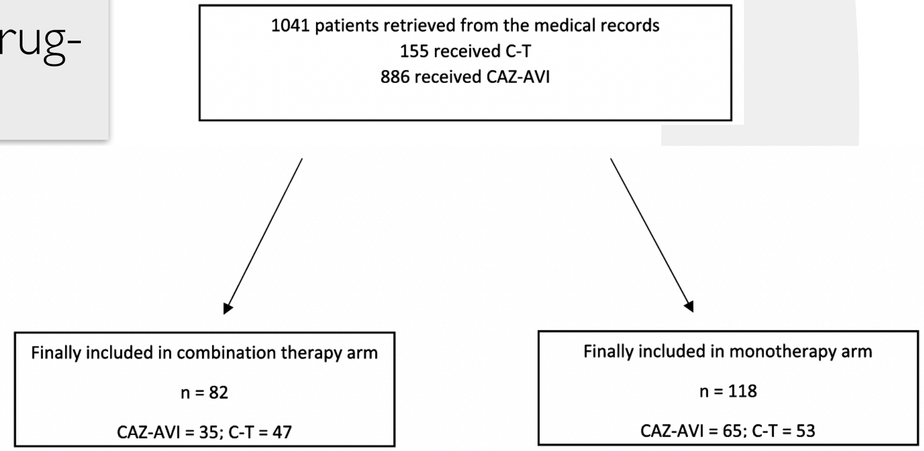
Almangour TA et al. *J Antimicrob Chemother* **2024**

Table 3
Subgroup analysis of the outcomes in patients who received monotherapy combination therapy.

Type of infection	Combination therapy (%)	Monotherapy (%)	*P*
HAP			
In-hospital mortality	50	44	0.
30-day mortality	35	22	0.
Clinical cure	50	61	0.
Wound			
In-hospital mortality	41	33	0.
30-day mortality	24	20	0.
Clinical cure	59	73	0.303
VAP			
In-hospital mortality	53	38	0.352
30-day mortality	24	29	0.725
Clinical cure	57	61	0.536
UTI			
In-hospital mortality	33	29	0.832
30-day mortality	17	14	0.891
Clinical cure	67	86	0.344
IAI			
In-hospital mortality	75	38	0.131
30-day mortality	67	38	0.248
Clinical cure	50	75	0.301

Abbreviation: HAP: hospital-acquired pneumonia; IAI: intraabdominal infection; UTI: urinary tract infection; VAP: ventilator-associated pneumonia.

HOWEVER, AKI (32% VS. 12%; P = 0.0006; OR, 3.45; 95% CI, 1.67–7.13) WAS SIGNIFICANTLY MORE COMMON IN PATIENTS WHO RECEIVED COMBINATION THERAPY



Result: ***118*** *patients and* ***82*** *patients were included in monotherapy and combination therapy arms, respectively. The cohort represented an ill population with* ***56****% in the intensive care unit and* ***37****% in septic shock. A total of* ***19****% of patients presented with bacteremia. Compared to monotherapy, combination therapy* ***did not significantly differ*** *in clinical cure (57% vs. 68%; P = 0.313; OR, 0.63; 95% CI, 0.36–1.14) in-hospital mortality (45% vs. 37%; P = 0.267; OR, 1.38; 95% CI, 0.78–2.45), or 30-day mortality (27% vs. 24%; P = 0.619; OR, 1.18; 95% CI, 0.62–1.25).*

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IAI			
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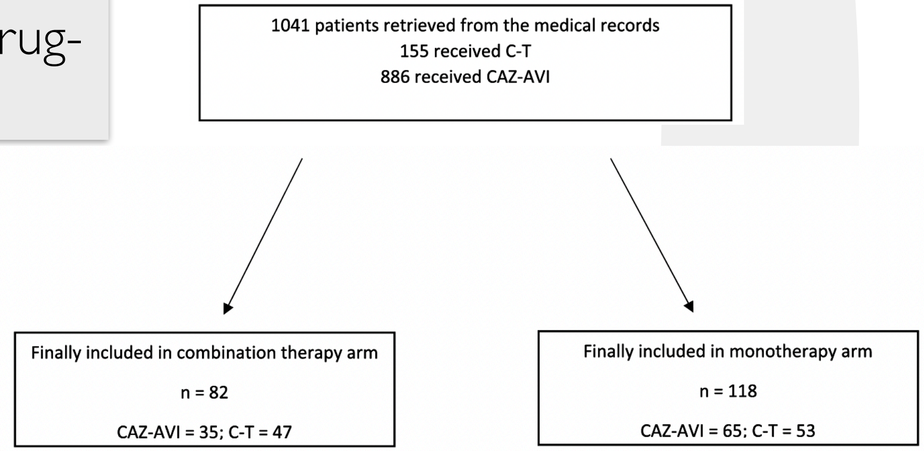
30-day mortality	67		
Clinical cure	50		

Abbreviation: HAP: hospital-acquired pneumonia; IAI: intraabdominal infection; UTI: urinary tract infection; VAP: ventilator-associated pneumonia.

*HOWEVER, **AKI** (32% VS. 12%; P = 0.0006; OR, 3.45; 95% CI, 1.67–7.13) WAS SIGNIFICANTLY*

In conclusion, this study showed that the two novel agents CAZ-AVI and C-T ***were not associated with better outcomes when used in combination with other antipseudomonal agents*** versus as monotherapy for the treatment of infections caused by multidrug-resistant *P. aeruginosa*. In the effort of reducing unnecessary antibiotic use, cost, and adverse effects, if the isolate is susceptible to the novel antipseudomonal agent being considered for treatment, monotherapy should be sufficient



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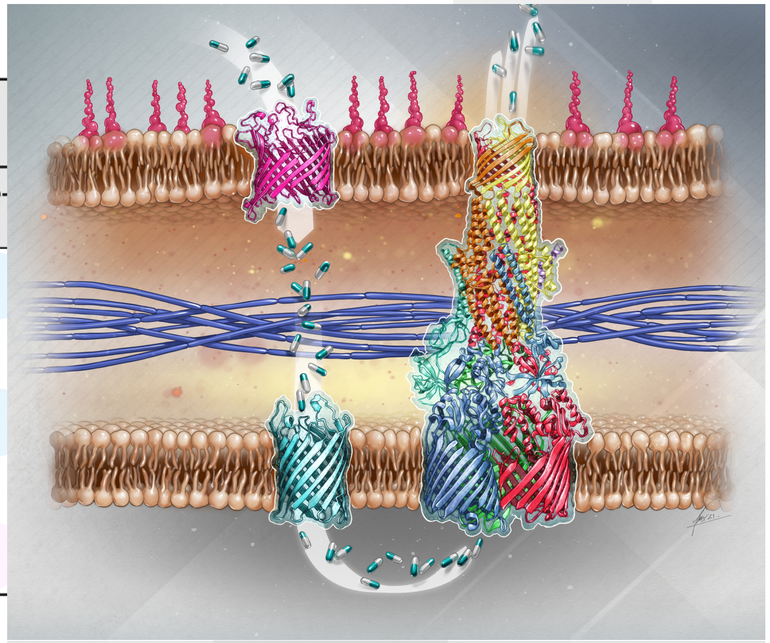
Ceftolozane: basis for potent anti-*Pseudomonas* activity

Wi YM. et al. *Antimicrob Agents Chemother* **2018**

TABLE 3 MIC range and resistance rates for ceftolozane-tazobactam and ceftazidime-avibactam according to results for resistance mechanisms among non-carbapenemase-producing CRPA clinical isolates

Resistance mechanism	No. of isolates	MIC range (median) (mg/liter)		% resistance	
		Ceftolozane-tazobactam	Ceftazidime-avibactam	Ceftolozane-tazobactam	Ceftazidime-avibactam
Decreased *oprD* expression	13	1–16 (2)	2–16 (4)	7.7	15.4
Decreased *oprD* and increased *mexB* expression[a]	9	1–4 (2)	2–32 (16)	0	55.6
Decreased *oprD* and increased *mexY* expression	1	1	2	0	0
Decreased *oprD* and increased *ampC* expression	3	1–4 (2)	4–8 (4)	0	0
Decreased *oprD* and increased *mexB* and *ampC* expression	4	2–32 (4)	8–16 (16)	25.0	50.0
Decreased *oprD* and increased *mexY* and *ampC* expression	1	2	16	0	100
Decreased *oprD* and increased *mexB*, *mexD*, and *ampC* expression	6	1–4 (2)	2–8 (4)	0	0
Decreased *oprD* and increased *mexB*, *mexY*, and *ampC* expression	2	2	8	0	0
Increased *mexB* expression	2	2	8–16	0	50
Increased *mexY* and *ampC* expression	1	4	16	0	100

[a]$P < 0.05$ in comparison of percent resistance to ceftolozane-tazobactam with that to ceftazidime-avibactam.

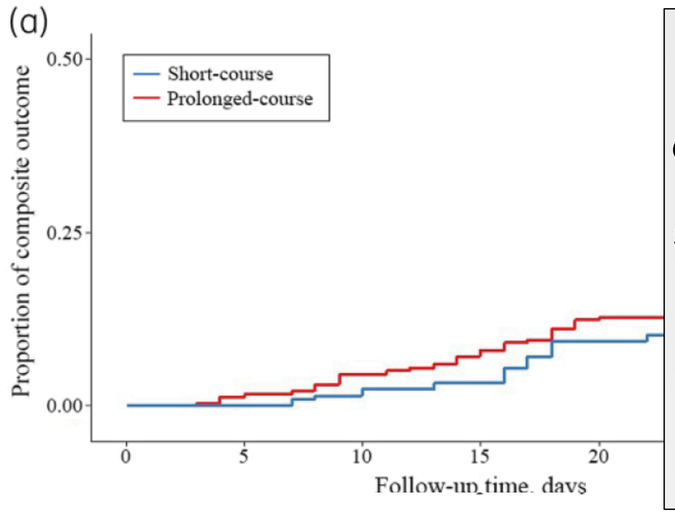


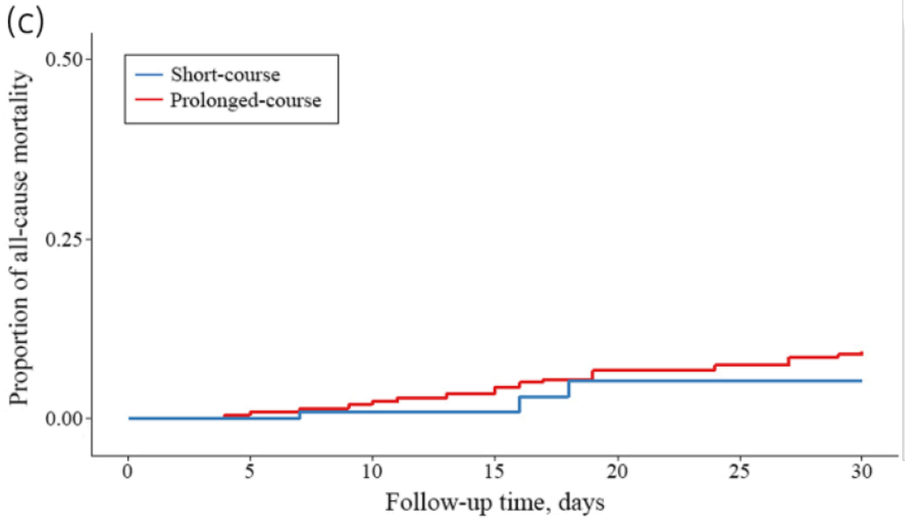
The C/T resistance rate was significantly lower than that of C/A among isolates showing decreased *oprD* and increased *mexB* expression (***5.1%*** versus ***25.6%***, P > 0.025, and ***4.3%*** versus ***34.8%***, P > 0.022, respectively)

Short versus ***prolonged*** courses of antimicrobial therapy for patients with uncomplicated *Pseudomonas aeruginosa* bloodstream infection: a retrospective study

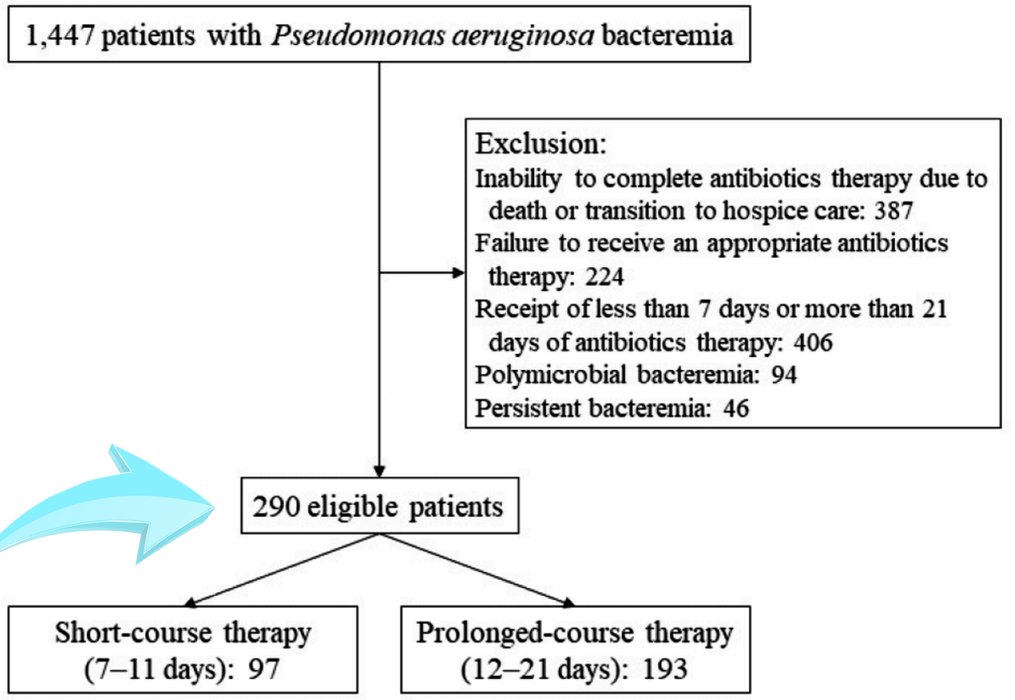
Bae M. et al. *J Antimicrob Agents* **2022**

METHODS: All patients with uncomplicated *P. aeruginosa* BSI admitted at a tertiary-care hospital from April 2010 to April 2020 were included. We compared the ***primary outcome*** (a composite of the rate of recurrent *P. aeruginosa* infection and mortality within 30 days after discontinuing antimicrobial therapy) among patients who underwent ***short*** (7–11 days) and ***prolonged*** (12–21 days) courses of antimicrobial therapy using propensity score analysis with the inverse probability of treatment weighting (IPTW) method





*We **suggest** that 7–11 days of antimicrobial therapy **is as effective as** the prolonged-course in treating those patients. Our findings reinforce the current tendency to lean toward shorter duration of antimicrobial*



Is ***short-course antibiotic therapy*** suitable for *Pseudomonas aeruginosa* bloodstream infections in onco-hematology patients with febrile neutropenia? Results of a multi-institutional analysis

Feng X. et al. *Clin Infect Dis* **2023**; 10.1093/cid/ciad605

BACKGROUND: several studies have suggested that short-course antibiotic therapy was effective in *Pseudomonas aeruginosa* (PA) bloodstream infections (BSI) in immunocompetent patients. While similar studies in patients with hematological malignancies were rare

RESULTS: *434* patients met eligibility criteria (short-course, 7-11 days, n=229; prolonged, 12-21 days, n=205). In the weighted cohort, ***the univariate and multivariate analysis*** indicated that ***short course antibiotic therapy had similar outcomes to the prolonged course***. The recurrent PA infection at any site or mortality within 30 days of completing therapy occurred in 8 (3.9%) patients in the short-course group and in 10 (4.9%) in the prolonged-course group (p = 0.979).

	Mortality or recurrent infection within 30 days			Fever relapse within 7 days			Recurrent infection within 90 days		
Characteristic	**no**	**yes**	**P value**	**no**	**yes**	**P value**	**no**	**yes**	**P value**
Monotherapy	209 (53.3)	6 (33.3)	0.156	199 (52.6)	16 (50.0)	0.918	200 (53.1)	15 (45.5)	0.512
MDR-PA	42 (10.7)	7 (38.9)	**<0.001**	41 (10.8)	8 (25.0)	**0.037**	39 (10.3)	10 (30.3)	**0.002**
CRPA	76 (19.4)	7 (38.9)	**0.044**	74 (19.6)	9 (28.1)	0.354	73 (19.4)	10 (30.3)	0.203

CONCLUSION

In the study, ***short-course therapy was non-inferior to prolonged-course therapy*** in terms of clinical outcomes. However, due to its biases and limitations, further prospective randomized controlled trials are needed to generalize our findings

Antibacterial effect of 7 days exposure to ***ceftolozane-tazobactam*** as monotherapy and in combo with fosfomycin or tobramycin against *Pseudomonas aeruginosa* with ceftolozane-tazobactam MICs at or above 4 mg/l in an in vitro PK model

Attwood M. et al. *J Antimicrob Chemother* **2023**;doi.org/10.1093/jac/dkad230

METHODS: an in vitro model was used to assess changes in bacterial load and population profiles after exposure to mean human serum concentrations of ***ceftolozane/tazobactam*** associated with doses of ***2 g/1 g q8h,*** ***fosfomycin*** concentrations associated with doses of ***8 g q8h*** or ***tobramycin*** at doses of ***7 mg/kg q24 h*** over 168 h

SUMMARY

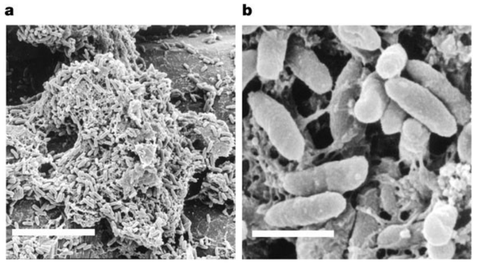
the addition of either fosfomycin or tobramycin to ceftolozane/tazobactam at simulated human clinically observed concentrations reduced *P. aeruginosa* bacterial loads and the risk of resistance to ceftolozane/tazobactam *when strains had ceftolozane/tazobactam MIC values at or above the clinical breakpoint*

Only in difficult strains of *Pseudomonas*

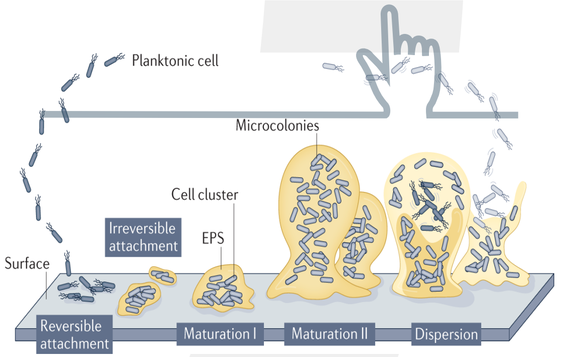
RESULTS: simulations of ceftolozane/tazobactam at 2 g/1 g q8h **ALONE** produced 3.5–4.5 log reductions in count by 6 h post drug exposure for strains with MIC ≤32 mg/L. The antibacterial effect over the first 24 h was related to ceftolozane/tazobactam MIC. There was subsequent regrowth with most strains to bacterial densities of $>10^6$ CFU/mL. Addition of either fosfomycin or tobramycin resulted in suppression of regrowth and in the case of **TOBRAMYCIN** more rapid initial bacterial killing up to 6 h. Changes in population profiles were noted with ceftolozane/tazobactam alone often after 96 h exposure but such changes were suppressed by fosfomycin and almost abolished by the addition of tobramycin

C/T plus ***tobramycin*** against free-floating and biofilm bacteria of hypermutable *Pseudomonas aeruginosa* epidemic strains: resistance mechanisms and synergistic activity

Agyeman AA. et al. *Int J* Antimicrob Agents **2023**

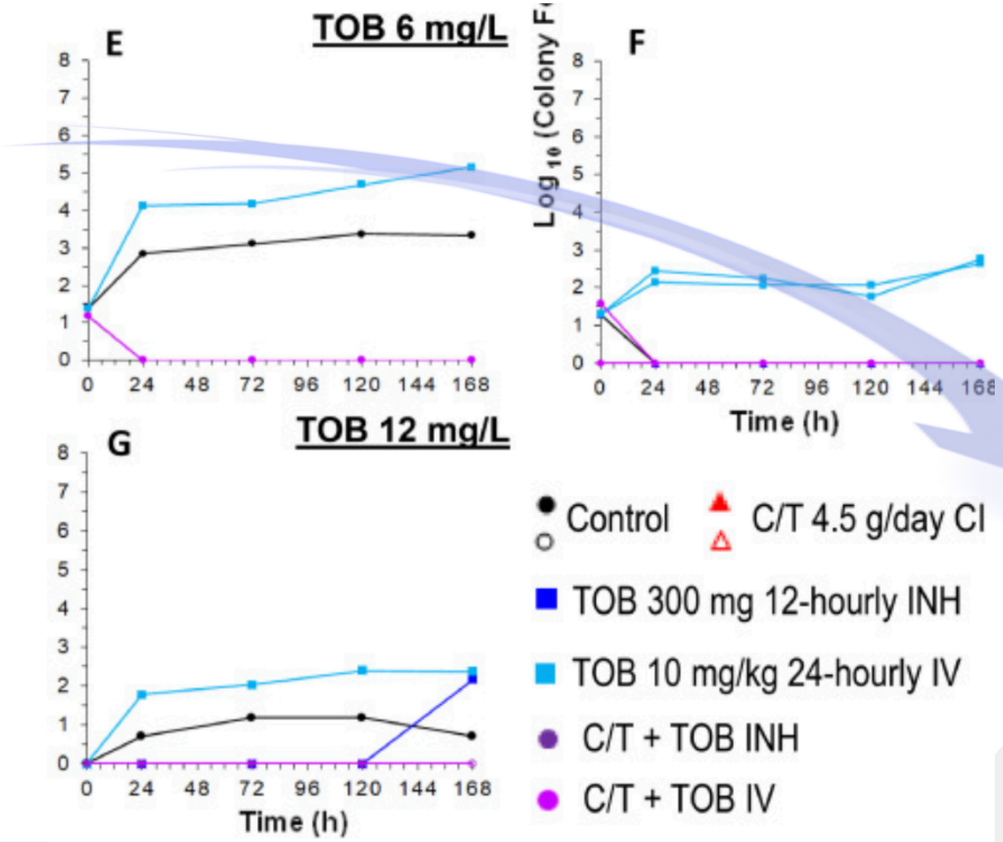


Sauer K. et al. *Nature Reviews Microbiol* **2022**; 20:608-620



In conclusion, we demonstrated that ***ceftolozane/tazobactam 4.5 g/day*** as continuous infusion in combination with ***tobramycin 300 mg q12h*** inhaled, or potentially ***tobramycin 10 mg/kg q24h IV***, may be a viable option for episodes of acute pulmonary exacerbations against *P. aeruginosa* epidemic strains in adolescents with CF

Only in difficult strains of *Pseudomonas*



The combination might be most useful against carbapenem-resistant, extensively drug-resistant isolates, when other treatment options are limited

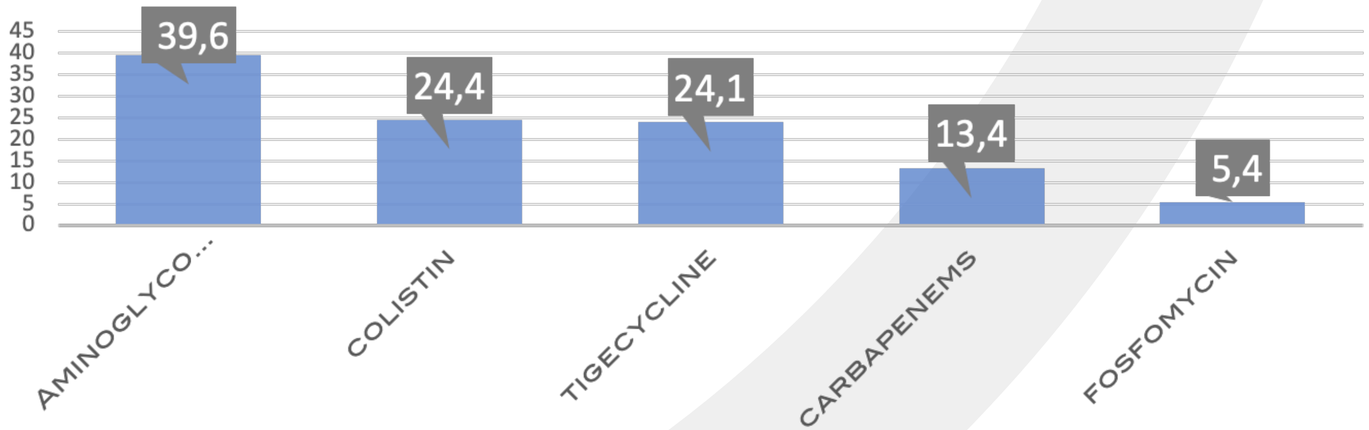
Mono vs. ***combo*** regimens with novel beta-lactam/beta-lactamase inhibitor combinations for the treatment of infections due to carbapenemase-producing *Enterobacterales*: insights from the literature

Meini S, Viaggi B, Tascini C. *Infection* **2021**

a **practical question** is whether these novel BLBLIs should be used as monotherapy or as part of a combination regimen with other antibiotics, and if so, with which ones, to reduce the emergence of resistant strains and to optimize their efficacy

Available evidence on combination therapy ***is scarce*** and mainly limited to retrospective studies involving 630 patients treated with CZA

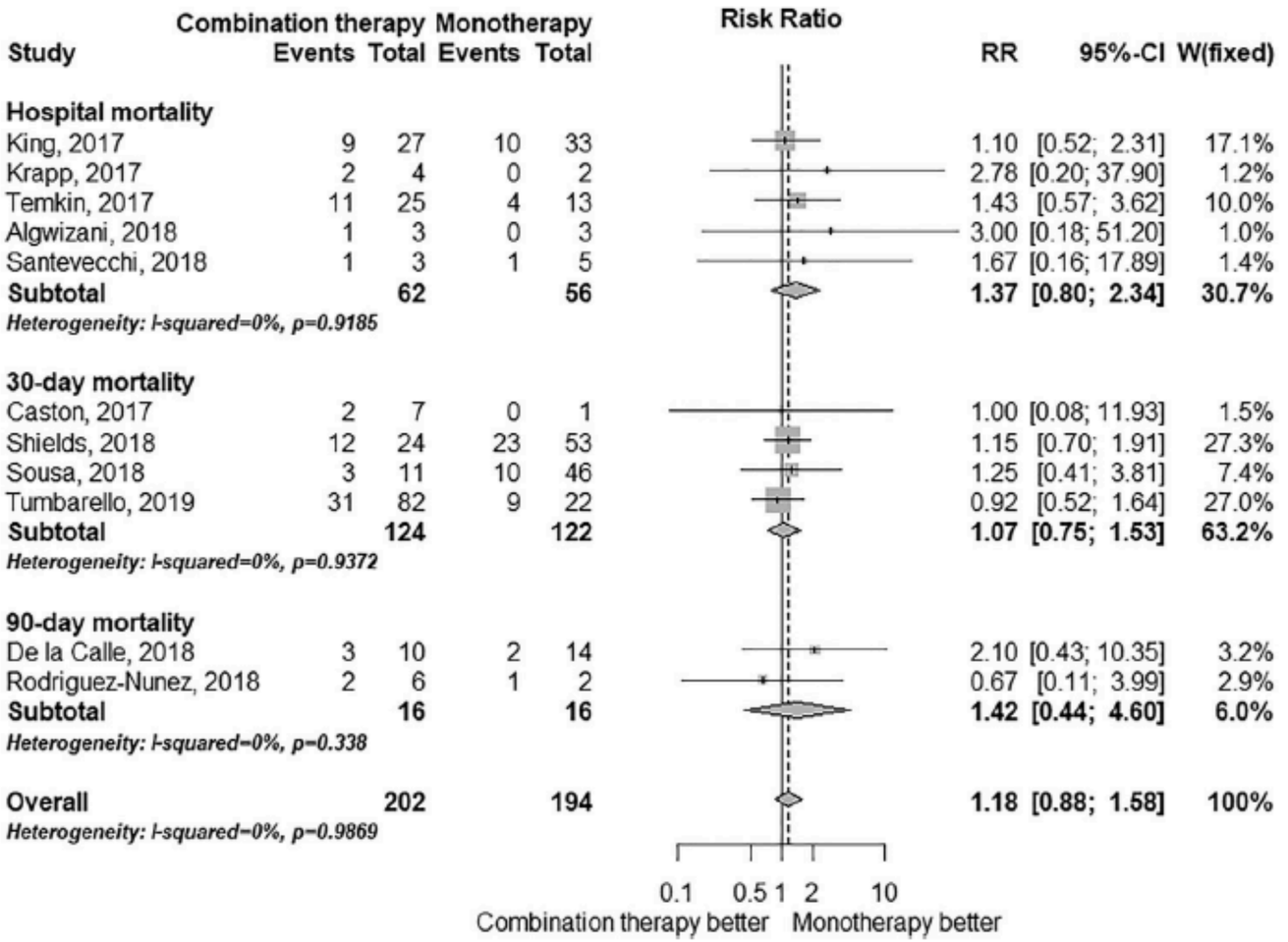
Currently, there is **NO DEFINITIVE EVIDENCE** whether combinations are more effective than monotherapies; further studies are warranted, and to date only personal opinions can be provided



Efficacy of ***CZA*** in monotherapy or combination therapy against carbapenem-resistant Gram-negative bacteria: A meta-analysis

Onorato L. et al. *Int J Antimicrob Agents* **2019**

*This meta-analysis suggests that use of ceftazidime/avibactam in monotherapy or combination therapy for infections due to CRE or CRPa could show a **similar effect** on mortality and microbiological cure rates. Studies on larger samples are needed to address this important issue*



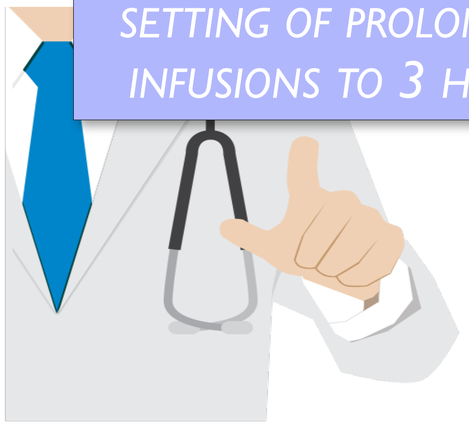
Ceftazidime-Avibactam Use for *Kbs. pneumoniae* Carbapenemase–Producing *Kbs. pneumoniae* Infections: A Retrospective Observational Multicenter Study

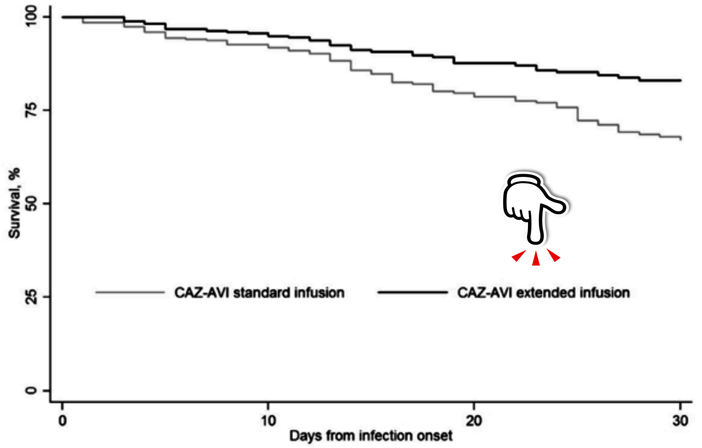
Tumbarello M. et al. *Clin Infect Dis* **2021**

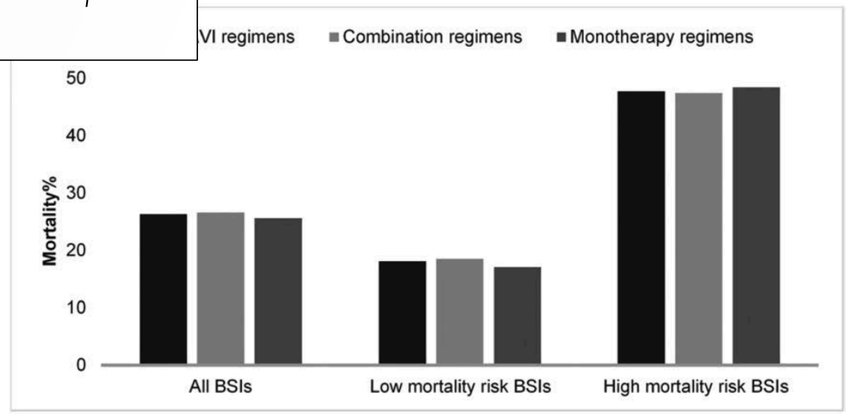
*The all-cause mortality rate 30 days after infection onset was **25%** (146/577). There **was no significant difference in mortality between patients managed with CAZ-AVI alone and those treated with combination regimens** (26.1% vs 25.0%, P = .79). In multivariate analysis, mortality was positively associated with presence at infection onset of septic shock (P = .002), neutropenia (P < .001), or an INCREMENT score ≥8 (P = .01); with lower respiratory tract infection (LRTI) (P = .04); and with CAZ-AVI dose adjustment for renal function (P = .01)*

577 adults with bloodstream infections (n = **391**) or nonbacteremic infections involving mainly the urinary tract, lower respiratory tract, and intra-abdominal structures. All received treatment with CAZ-AVI alone (n = **165**) or with≥1 other active antimicrobials (n = **412**)

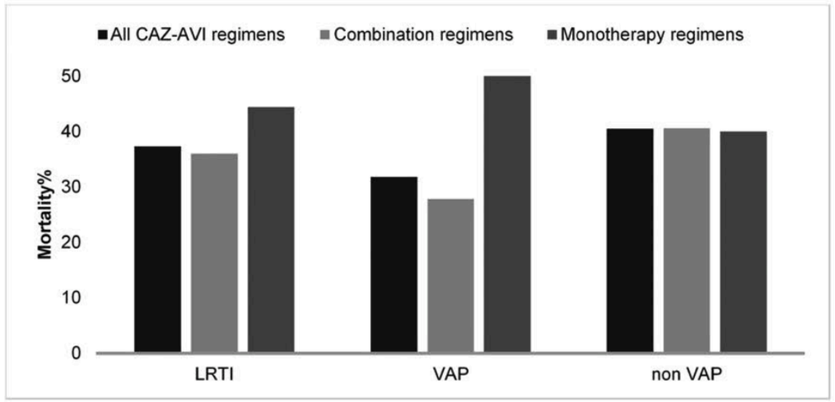
FURTHER STUDY IS NEEDED TO EXPLORE FACTORS CONTRIBUTING TO THE DRUG'S SEEMINGLY MORE LIMITED EFFICACY IN LRTIS AND THE POTENTIAL SURVIVAL BENEFITS IN THIS SETTING OF PROLONGING CAZ-AVI INFUSIONS TO 3 HOURS OR MORE







B



KPC

Meropenem Vaborbactam

2.2g q8h
Extended Infusion - 3h

loading dose

Imipenem Relebactam

0.5/0.5/0.5g q8h
Extended Infusion - 1.5h

loading dose

Ceftazidime Avibactam + **Fosfomycin**

2.5g q8h
Continous Infusion

loading dose

4g q6h
Continous Infusion

Antibiotico	MIC mg/l
Amoxicillina/clavulanato	>64 R
Piperacillina/tazobactam	>128 R
Ceftiaxone	>4 R
Ceftazidime	>128 R
Cefepime	>32 R
Meropenem	>64 R
Fosfomicina	32 S
Amikacina	8 S
Gentamicina	>8 R
Ciprofloxacina	>4 R
Colistina	>8 R
CZA	16 R
MVB	32 R
CFD	2 S

K. pneumoniae KPC-3
IPERESPRESSA

Cefiderocol

2g q8h
Continous Infusion

loading dose

IVAC caused by *Enterobacterales* ***KPC +*** in critically ill adult ptz

Gatti M, Viaggi B, Rossolini GM, Pea F, Viale P
Exp Rev Anti Infect Ther Sep **2022**
Infect Drug Resist Jun **2021**
Antibiotics dec **2021**

KPC

1 Ceftazidime Avibactam

2.5g q8h
Continous Infusion
loading dose

1 Meropenem Vaborbactam

2.2g q8h
Extended Infusion - 3h
loading dose

1 Imipenem Relebactam

0.5/0.5/0.5g q8h
Extended Infusion - 1.5h
loading dose

Antibiotico	MIC mg/l
Amoxicillina/clavulanato	>64 R
Piperacillina/tazobactam	>128 R
Ceftiaxone	>4 R
Ceftazidime	>128 R
Cefepime	>32 R
Meropenem	>64 R
Fosfomicina	32 S
Amikacina	8 S
Gentamicina	>8 R
Ciprofloxacina	>4 R
Colistina	>8 R
CZA	16 R
MVB	32 R
CFD	2 S

K. pneumoniae KPC-3
IPERESPRESSA

1 Cefiderocol

2g q8h
Continous Infusion
loading dose

BSI caused by
Enterobacterales ***KPC +***
in critically ill adult ptz

Gatti M, Viaggi B, Rossolini GM, Pea F, Viale P
Exp Rev Anti Infect Ther Sep **2022**
Infect Drug Resist Jun **2021**
Antibiotics dec **2021**

VIM

KNOWLEDGE RESISTANCE

1

Cefiderocol

2g q8h
Continous Infusion

loading dose

NDM

1

Ceftazidime Avibactam + **Aztreonam**

2.5g q8h
Continous Infusion

loading dose

2g q8h
Continous Infusion

2g q6h
Continous Infusion

MAYBE?

Imipenem Relebactam + **Aztreonam**

0.5/0.5/0.5g q8h
Extended Infusion - 1.5h

loading dose

2g q8h
Continous Infusion

2g q6h
Continous Infusion

2

Cefiderocol

2g q8h
Continous Infusion

loading dose

bla_{NDM-1}, $bla_{CTX-M-15}$, *ΔcirA*

Antibiotico	MIC
Amoxi/clav	>64 R
Piperacillina/tazobactam	128 R
Ceftriaxone	≥4 R
Ceftazidime	>64 R
Cefepime	>16 R
Imipenem	>16 R
Meropenem	>16R
C/T	>32R
Fosfomicina	16 S
Amikacina	>16 R
Gentamicina	>8 R
Ciprofloxacina	>4 R
Colistina	>4 R
CAZ/AVI	>64 R
MEM/VAB	ND
I/R	ND
Cefiderocol	128 R

Gatti M, Viaggi B, Rossolini GM, Pea F, Viale P.
Exp Rev Anti Infect Ther Sep **2022**
Infect Drug Resist Jun **2021**
Antibiotics dec **2021**

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)

- For patients with severe infections due to CRE-carrying metallo-β-lactamases (MBL) and/or resistant to all other antibiotics, including ceftazidime-avibactam and meropenem-vaborbactam,

we conditionally recommend treatment with cefiderocol (**conditional recommendation for use, low certainty of evidence**).

Paul M. et al. *Clin Microbiol Infect* **2022**

CMI CLINICAL MICROBIOLOGY AND INFECTION

CARBA-R

1

Cefiderocol

2g q8h
Continous Infusion
loading dose

Cefiderocol

+

Ampicillin/ Sulbactam

MAYBE?

4g q6h
Continous Infusion
loading dose

2

Fosfomycin — 4g q6h Continous Infusion

+

Ampicillin/ Sulbactam — 4g q6h Continous Infusion *loading dose*

Antibiotico	MIC mg/l
Amikacina	>16R
Ciprofloxacina	>1 R
Meropenem	>64R
Gentamicina	>8 R
Tigeciclina	1
Colistina	>4 R

DURLOBACTAM is a potent inhibitor of class A, C, and D serine β-lactamases. The key differentiating feature as compared to other DBO BLIs ***is its activity against class D carbapenemases of the OXA family,*** which are prevalent in *A. baumannii*

Durlobactam, a New DBO β-Lactamase Inhibitor for the Treatment of *Acinetobacter* Infections in Combination With ***Sulbactam***

Shapiro AB. et al. *Front in Microbiol* **2021**

In addition to inhibiting β-lactamases, some DBO β-lactamase inhibitors also exhibit intrinsic antibacterial activity due to inhibition of PBP2. ***Durlobactam predominantly inhibits PBP2*** of *A. baumannii*

IVAC/BSI caused by *Acinetobacter baumannii* in critically ill adult ptz

Gatti M, Viaggi B, Rossolini GM, Pea F, Viale P
Exp Rev Anti Infect Ther Sep **2022**
Infect Drug Resist Jun **2021**
Antibiotics dec **2021**

Sulbactam Its inhibitory activity is limited to a subset of class A serine β-

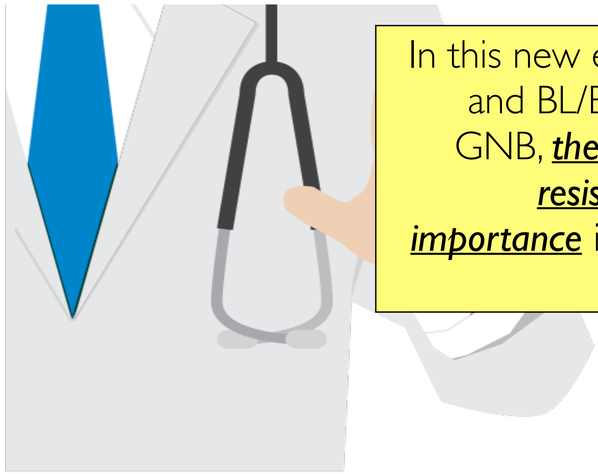
A unique feature of sulbactam is its intrinsic antibacterial activity against *Acinetobacter* and a limited number of other bacterial species, which results from its inhibition of key enzymes required for bacterial peptidoglycan synthesis. ***PBP1a, PBP1b,*** and ***PBP3***, but not PBP2, are targets of sulbactam in *Acinetobacter* species

Coverage of CPE by new beta-lactamase inhibitor combinations (*BLICs*) and new beta-lactams

Anti-CPE agents exhibit different activity profiles *vs*. strains producing different enzymes: importance to detect the resistance mechanism

Mechanism	CAZ/AVI	MER/VAB	TOL/TAZ	IMI/REL	ATM/AVI	FEP/TANI	FEP/ZIDE	FEP/ENM	MER/NACU	CFDC	ERV	PLZ
KPC	+/-	+/-	-	+	+	+	+	+/-	+	+/-	+	+
OXA-48	+	-	-	+	+	+	+	+	+	+	+	+
VIM	-	-	-	-	+	+	+	-	+/-	+	+	+
NDM	-	-	-	-	+	+	+	-	+/-	+/-	+/-	-
IMP	-	-	-	-	+	-	?	-	+/-	+	+	+

Bush & Bradford. *Cold Spring Harb Perspect Med.* **2016**; 6(8). pii: a025247- Pogue et al. *Clin Infect Dis* **2019** - Choi & McCarthy *Exp Op Invest Drugs* 27:2, 193-197 - Thomson et al. *Antibiotics* **2019**; 8:32 - Mushtaq et al. *JAC* **2019**; 74:953 - www.venatorx.com - Le Terrier C. et al. *Antimicrob Agents Chemother* **2023**



In this new era of renewed activity of BL and BL/BLI combinations against CR-GNB, ***the determinants of carbapenem resistance have assumed a crucial importance*** in guiding both empirical and targeted therapies

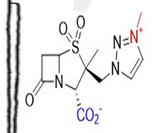
Giacobbe DR. et al. *Future Microbiol* **2022**

emother may **2022**

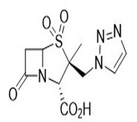
ESBL gene
ression of the
ere the isolates
BL producers

Vázquez-Ucha JC. *Antimicrob Agents Chemother* may **2022**

New MICs of cefepime and cefepime/enmetazobactam for KPC-carrying isolates are determined by the clonality of the isolates



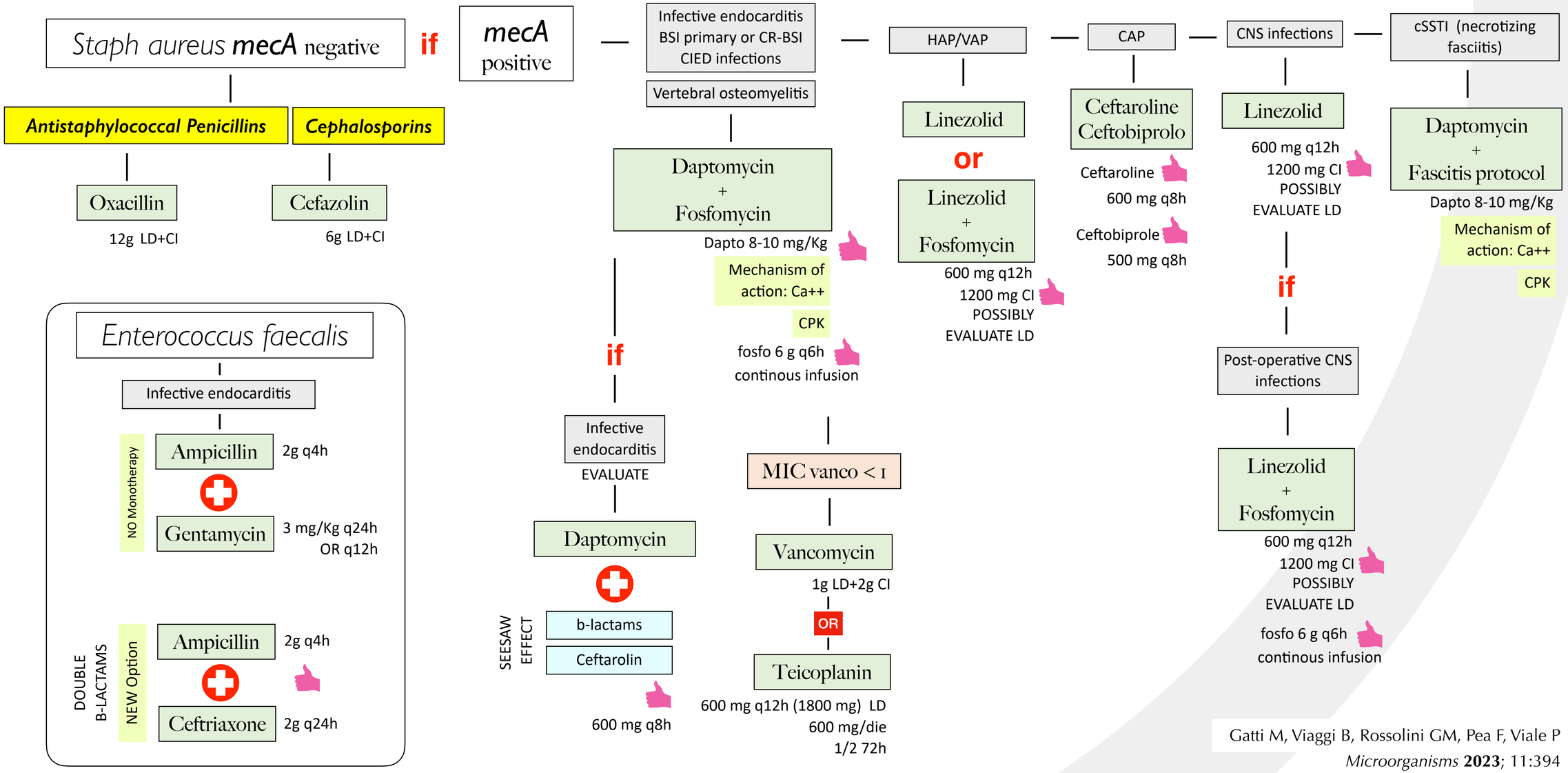
Enmetazobactam



Tazobactam

The non-ESBL-producing *K. pneumoniae* isolates mostly belong to sequence type 512 (**ST512**), whereas the KPC- and ESBL-producing isolates mostly belong to **ST307**

Flowchart for ***diagnosis*** and ***treatment*** of infections caused by Gram positive in ICU

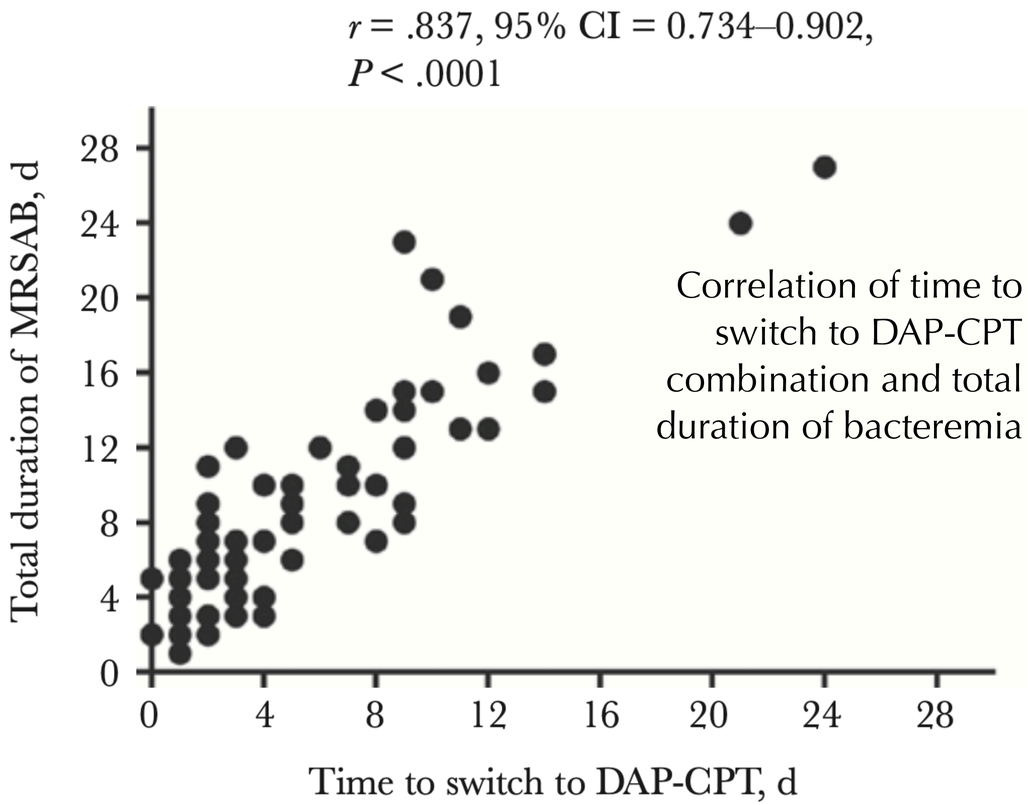


Gatti M, Viaggi B, Rossolini GM, Pea F, Viale P
Microorganisms **2023**; 11:394

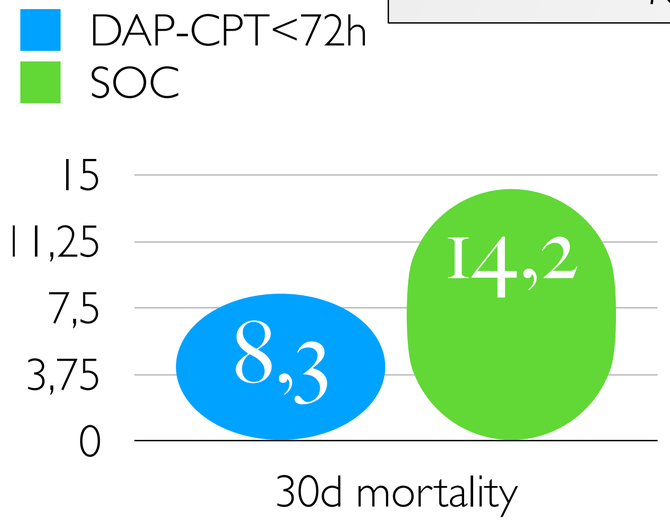
Multicenter Cohort of Patients With Methicillin-Resistant *Staphylococcus aureus* Bacteremia Receiving ***Daptomycin*** Plus ***Ceftaroline*** Compared With Other MRSA Treatments

58 patients received DAP-CPT with 113 matched SOC

McCreavy EK. et al. *Open Forum Infect Dis* **2020**

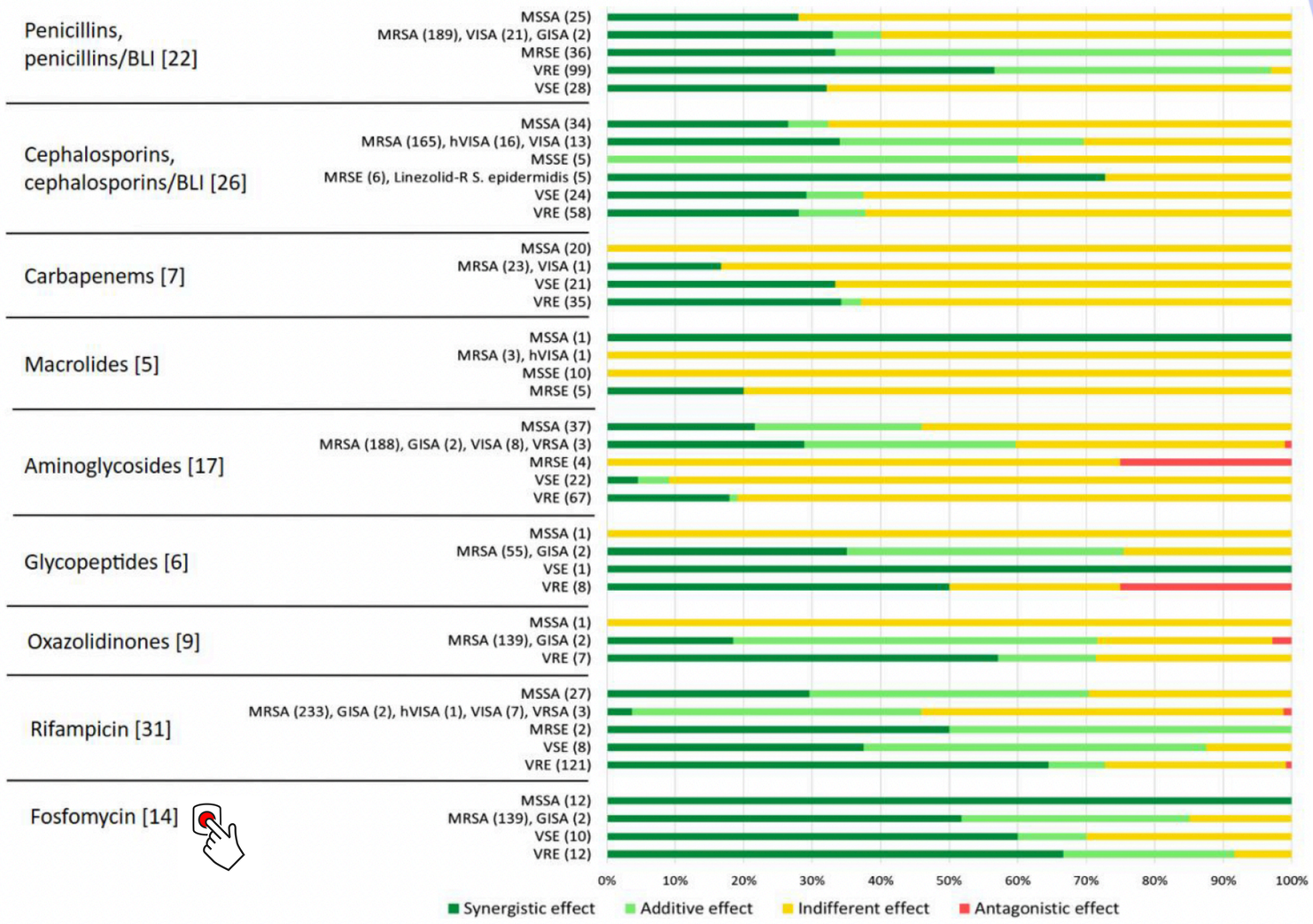


*These data **also support** the potentially **DAP-sparing** **effect of CPT synergy** and opportunity for combination de-escalation, as our combination group received a mean 8.2-mg/kg/d DAP, as op- posed to the guideline-recommended option of 10 mg/kg/d*



Daptomycin synergistic properties from *in vitro* and *in vivo* studies: a systematic review

Antonello RM. et al. *J Antimicrob Chemother* **2023**; 78:52-77



RESULTS: A total of 92 studies and ***1087*** isolates (723 *Staphylococcus aureus*, 68 *Staphylococcus epidermidis*, 179 Enterococcus faecium, 105 *Enterococcus faecalis*, 12 *Enterococcus durans*) were included. ***Synergism*** accounted for ***30.9%*** of total interactions, while indifferent effect was the most frequently observed interaction (***41.9%***). Antagonistic effect accounted for 0.7% of total interactions. The highest synergistic rates against *S. aureus* were observed with daptomycin in combination with fosfomycin (***55.6%***). For *S. epidermidis* and *Enterococcus* spp., the most effective combinations were daptomycin plus ceftobiprole (***50%***) and daptomycin plus fosfomycin (***63.6%***) or rifampicin (***62.8%***), respectively.

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