LA TERAPIA DI COMBINAZIONE ANTIBATTERICA: PRO E CONTRO Le infezioni da *Pseudomonas aeruginosa*

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Disclosures (past 5 years)

Advisor/consultant/speaker bureau

- Angelini, Gilead, Menarini, MSD, Pfizer, Shionogi



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1- Concepts of Pseudomonas aeruginosa



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Pseudomonas aeruginosa General concept

Gram-negative non-fermentative bacillus. One of the most frequent causes of severe nosocomial infections (especially ICU and immunocompromised patients)

First cause of VAP and burn wound infections: *P.aeruginosa* is associated with very high mortality rates

Most frequent driver of chronic respiratory infections in CF. **Extraordinary capacity for developing resistance**



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Pseudomonas aeruginosa infections



VAP

- BSI

Wound/Burn infections

UTIS Related to bladder catheter

Peritonitis (tertiary>>> secondary)



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Sepsis in European intensive care units: Results of the SOAP study

Vincent JL Critical care Medicine 2006

- 3.147 adult patiens (64 yrs) from 198 ICU
- 1,177 (37.4%) had sepsis (lung>>> abdomen).
- Common organisms:
 - ➢ S. aureus 30%
 - Pseudomonas species 14%
 - *≻ E. coli* 13%



	OR (95% CI)	p Value
SAPS II score ^{a} (per point increase)	1.0(1.0-1.1)	<.001
Age (per year increase)	1.1 (1.0-1.1) 1.0 (1.0-1.0) 1.1 (1.0 1.1)	.001
Blood stream infection	1.1 (1.0-1.1) 1.7 (1.2-2.4)	.002
Pseudomonas infection	2.4 (1.3-4.5) $1.6 (1.1-2.4)$.008
Medical admission Female gender	$1.4 (1.0-1.8) \\ 1.4 (1.0-1.8)$	$.049\\.044$

2- Rationale for combination therapy in *P.aeruginosa* infections



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Rationale for combination therapy in *P.aeruginosa* infections

Increase the probability of adequate empirical therapy?





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

183 episodes of 1,0monomicrobial combination therapy P.aeruginosa VAP monotherapy 0,8survival Adequate empirical combo tx inadequate Adequate empirical mono tx therapy 0,6-**Empirical therapy:** Cumulative 63.3% combo vs 36.6% 0,4-Mono Inadequate Tx 0,2-Adequate empirical therapy: 105/116 0,0-(90.5%) **combo** vs 28/67 0.00 50.00 100.00 150.00 200.00 (56.7%) mono, *p<0.001.* Hospital stay (days)

Garnacho-Montero et al. Crit Care Med 2007



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When *P.aeruginosa* should be included in the empirical therapy?

- HCAP in patients with bronchectasis and/or multiple courses of antimicobials in the past months
- Post-operative peritonitis or HCA-IAI + septic shock
- Late-onset nosocomial infections
 - Septic shock
 - Severe immune deficiencies
 - Very old
 - Device usage
 - The ecology of the unit
 - Previous colonization
 - Previous broad spectrum antibiotic therapy



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Combination therapy: when?

• HAP / VAP / septic shock

Empiric

- Pts at risk for MDR
 - High risk of *P. aeruginosa*

The antimicrobial regimen should be promptly narrowed or discontinued based on culture and susceptibility profile results and on clinical stability

Tar	rgeted	 P. aeruginosa: Only in empiric initial treatment A. baumannii? K. pneumoniae (KPC) 				
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Empirical treatment of severe Pseudomonas aeruginosa infection.

- •Underlying comorbidities (neutropenia, severe immunosuppression, structural lung disease, solid tumour)
- •Previous colonization by MDR/XDR P. aeruginosa strain
- •Previous therapy (within 3 months) with an antipseudomonal β-lactam
- •Hospital setting with a prevalence >15-20% of MDR P. aeruginosa
- •Clinical criteria for sepsis or septic shock?

YES (at any)

BACKBONE DRUG

Ceftolozane- tazobactam > ceftazidimeavibactam> meropenem> piperacillintazovactam/ ceftazidime/ cefepime **PLUS**

SECOND ANTI-PSEUDOMONAL AGENT Aminoglycoside/ colistin/ fosfomycin> fluoroquinolones BACKBONE DRUG Piperacillin/tazobactam/ carbapenem (maily meropenem)/ ceftazidime/ cefepime

NO (to all)

Bassetti M et al. Curr Opin Infect Dis. 2018;31(6):578-586.



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ANTI-PSEUDOMONAL BETA-LACTAM

+ Fluoroquinolone or aminoglycoside iv/ae or Colistin iv + aerosol

> + Aminoglycoside or colistin or fosfomycin

+ Aminoglycoside or colistin

Ospedale Policlinico San Martino IRCCS Genoa, Italy





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di Genova ize della Salute (DISSAL)

Rationale for combination therapy in *P.aeruginosa* infections

- Increase the probability of adequate empirical therapy? Maybe yes but promptly tailor abx based on AST
- In vivo synergistic activity that might improve clinical outcome?





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iDIAPASON trial

Impact of appropriate mono vs combo definitive therapy on 90-day mortality

- 169 patients with VAP due to P.aeruginosa
- Monotherapy_(n=94) vs
 Combo (n=75)
- ICU mortality: Monotherapy 18.1% vs Combo 26.7% (p=0.18)
- <u>No differences</u> between groups in terms of other patient-centered outcomes recurrence of VAP and development of MDR pathogens



Foucrier A; Crit Care 2023



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Single vs double active combination (DACT) in septic shock

Subgroup adjusted OR (95% CI) P value adjusted OR (95% CI) P value adjusted OR (95% CI) P value Neutropenia (N = 69)° DACT 0.36 (0.11-1.23) 0.103 0.29 (0.09-0.92) 0.036 0.25 (0.08-0.79) 0.4 PS 1.27 (0.09-18.16) 0.862 1.13 (0.09-13.92) 0.923 4.22 (0.34-52.16) 0.4 Haematological malignancy (N = 89) DACT 0.74 (0.23-2.35) 0.609 0.45 (0.15-1.32) 0.144 0.45 (0.16-1.29) 0.1 DACT 0.74 (0.23-2.35) 0.609 0.45 (0.15-1.32) 0.144 0.45 (0.16-1.29) 0.1 Unknown focus of infections (N = 94) DACT 0.47 (0.17-1.28) 0.139 0.39 (0.15-1.03) 0.056 0.44 (0.17-1.14) 0.40 DACT 0.47 (0.17-1.28) 0.139 0.39 (0.15-1.03) 0.061 0.03 (0.01-0.33) 0.40 Plumonary focus of infections (N = 98) DACT 0.89 (0.34-2.31) 0.804 0.88 (0.36-2.18) 0.782 0.68 (0.28-1.65) 0.35 DACT 0.89 (0.34-2.31) 0.354 </th <th></th> <th colspan="2">7 day mortality</th> <th colspan="2">15 day mortality</th> <th colspan="2">30 day mortality</th>		7 day mortality		15 day mortality		30 day mortality	
Neutropenia (N = 69) ^o DACT 0.36 (0.11-1.23) 0.103 0.29 (0.09-0.92) 0.036 0.25 (0.08-0.79) 0.4 PS 1.27 (0.09-18.16) 0.862 1.13 (0.09-13.92) 0.923 4.22 (0.34-52.16) 0.5 Haematological malignancy (N = 89) DACT 0.74 (0.23-2.35) 0.609 0.45 (0.15-1.32) 0.144 0.45 (0.16-1.29) 0.5 PS 0.43 (0.03-5.44) 0.514 0.34 (0.03-3.76) 0.380 0.47 (0.05-4.74) 0.5 PS 0.43 (0.03-5.44) 0.514 0.39 (0.15-1.03) 0.056 0.44 (0.17-1.14) 0.6 PS 0.09 (0.01-0.99) 0.049 0.05 (0.01-0.52) 0.013 0.03 (0.01-0.33) 0.6 Pulmonary focus of infections (N = 98) DACT 0.89 (0.34-2.31) 0.804 0.88 (0.36-2.18) 0.782 0.68 (0.28-1.65) 0.3 PS 0.32 (0.03-3.56) 0.354 0.31 (0.03-3.11) 0.321 0.57 (0.06-5.38) 0.6 PS 0.32 (0.03-3.56) 0.354 0.31 (0.03-3.11) 0.321 0.57 (0.06-5.38) 0.6 Ps 0.14 (0.02-0.95) 0.044 0.06 (0.01-0.44) 0.005 0.09 (0.02-0.56) 0.7 PS 0.14 (0.02-0.95) 0.044 0.06 (0.01-0.44) 0.005 0.09 (0.02-0.56) 0.7 Ps 0.14 (0.02-0.95) 0.044 0.06 (0.01-0.44) 0.005 0.09 (0.02-0.56) 0.7 Ps 0.12 (0.02-0.70) 0.018 0.34 (0.09-1.27) 0.107 0.26 (0.08-0.92) 0.7 Ps 0.12 (0.02-0.70) 0.018 0.34 (0.09-1.27) 0.107 0.26 (0.08-0.92) 0.7 Ps 0.12 (0.02-0.70) 0.018 0.34 (0.09-1.27) 0.107 0.26 (0.08-0.92) 0.7 Ps 0.12 (0.02-0.70) 0.018 0.34 (0.09-1.27) 0.107 0.26 (0.08-0.92) 0.7 Ps 0.12 (0.02-0.70) 0.018 0.34 (0.09-1.27) 0.107 0.26 (0.08-0.92) 0.7 Ps 0.12 (0.02-0.70) 0.018 0.34 (0.09-1.27) 0.107 0.26 (0.08-0.92) 0.7 Ps 0.12 (0.02-0.70) 0.018 0.34 (0.09-1.27) 0.107 0.26 (0.08-0.92) 0.7 Ps 0.12 (0.02-0.70) 0.018 0.34 (0.09-1.27) 0.107 0.26 (0.08-0.92) 0.7 Ps 0.21 (0.02-0.70) 0.018 0.34 (0.09-1.27) 0.107 0.26 (0.08-0.92) 0.7 Ps 0.21 (0.02-0.70) 0.018 0.34 (0.09-1.27) 0.107 0.26 (0.08-0.92) 0.7 Ps 0.21 (0.02-0.70) 0.018 0.34 (0.09-1.27) 0.107 0.26 (0.08-0.92) 0.7 Ps 0.25 (0.08 0.92) 0.7 Ps 0.25 (0.08 0.92) 0.7 Ps 0.26 (0.08 0.92) 0.7 Ps	Subgroup	adjusted OR (95% CI)	P value	adjusted OR (95% CI)	<i>P</i> value	adjusted OR (95% CI)	P value
DACT 0.36 (0.11-1.23) 0.103 0.29 (0.09-0.92) 0.036 0.25 (0.08-0.79) 0.4 PS 1.27 (0.09-18.16) 0.862 1.13 (0.09-13.92) 0.923 4.22 (0.34-52.16) 0.5 Haematological malignancy (N = 89) 0.43 (0.03-5.44) 0.514 0.34 (0.03-3.76) 0.380 0.47 (0.05-4.74) 0.5 DACT 0.43 (0.03-5.44) 0.514 0.39 (0.15-1.03) 0.056 0.44 (0.17-1.14) 0.0 DACT 0.47 (0.17-1.28) 0.139 0.39 (0.15-1.03) 0.056 0.44 (0.17-1.14) 0.0 DACT 0.47 (0.17-1.28) 0.139 0.39 (0.15-1.03) 0.056 0.44 (0.17-1.14) 0.0 PS 0.09 (0.01-0.99) 0.049 0.05 (0.01-0.52) 0.013 0.03 (0.01-0.33) 0.0 Pulmonary focus of infections (N = 98) 0.25 (0.03-3.56) 0.354 0.31 (0.03-3.11) 0.321 0.57 (0.06-5.38) 0.6 DACT 0.60 (.25-1.44) 0.251 0.75 (0.32-1.76) 0.501 0.86 (0.38-1.95) 0.7 PS 0.14 (0.02-0.95) 0.044 0.06 (0.01-0.44) 0.005 0.09 (0.02-0.56) 0.0	Neutropenia (N = 69)ª						
PS 1.27 (0.09–18.16) 0.862 1.13 (0.09–13.92) 0.923 4.22 (0.34–52.16) 0.1 Haematological malignancy (N = 89) DACT 0.74 (0.23–2.35) 0.609 0.45 (0.15–1.32) 0.144 0.45 (0.16–1.29) 0.7 PS 0.43 (0.03–5.44) 0.514 0.34 (0.03–3.76) 0.380 0.47 (0.05–4.74) 0.5 Unknown focus of infections (N = 94) 0.47 (0.17–1.28) 0.139 0.39 (0.15–1.03) 0.056 0.44 (0.17–1.14) 0.0 PS 0.09 (0.01–0.99) 0.049 0.05 (0.01–0.52) 0.013 0.03 (0.01–0.33) 0.0 Pulmonary focus of infections (N = 98) 0.32 (0.03–3.56) 0.354 0.31 (0.03–3.11) 0.321 0.57 (0.06–5.38) 0.6 DACT 0.89 (0.34–2.31) 0.804 0.88 (0.36–2.18) 0.782 0.68 (0.38–1.65) 0.3 DACT 0.32 (0.03–3.56) 0.354 0.31 (0.03–3.11) 0.321 0.57 (0.06–5.38) 0.6 PS 0.32 (0.02–0.70) 0.044 0.06 (0.01–0.44) 0.005 0.09 (0.02–0.56) 0.3 DACT 0.60 (.25–1.44) 0.251 0.75 (0.32–1.76) 0.501 0.86 (0.38–1.95	DACT	0.36 (0.11-1.23)	0.103	0.29 (0.09-0.92)	0.036	0.25 (0.08-0.79)	0.019
Haematological malignancy (N = 89) DACT 0.74 (0.23–2.35) 0.609 0.45 (0.15–1.32) 0.144 0.45 (0.16–1.29) 0.7 PS 0.43 (0.03–5.44) 0.514 0.34 (0.03–3.76) 0.380 0.47 (0.05–4.74) 0.5 Unknown focus of infections (N = 94) DACT 0.47 (0.17–1.28) 0.139 0.39 (0.15–1.03) 0.056 0.44 (0.17–1.14) 0.0 PS 0.09 (0.01–0.99) 0.049 0.05 (0.01–0.52) 0.013 0.03 (0.01–0.33) 0.0 Pulmonary focus of infections (N = 98) DACT 0.89 (0.34–2.31) 0.804 0.88 (0.36–2.18) 0.782 0.68 (0.28–1.65) 0.3 PS 0.32 (0.03–3.56) 0.354 0.31 (0.03–3.11) 0.321 0.57 (0.06–5.38) 0.6 Time to blood culture positivity <7.5 h (N = 139) DACT 0.60 (.25–1.44) 0.251 0.75 (0.32–1.76) 0.501 0.86 (0.38–1.95) 0.7 PS 0.14 (0.02–0.95) 0.044 0.06 (0.01–0.44) 0.005 0.09 (0.02–0.56) 0.7 PS 0.12 (0.02–0.70) 0.018 0.34 (0.09–1.27) 0.107 0.26 (0.08–0.92) 0.0 PS 82.18 (1.71–3952.63 0.026 6.79 (0.38–122.12) 0.194 8.79 (0.56–136.83) 0.7 PACT 0.84 (0.49–1.44) 0.528 0.85 (0.52–1.39) 0.516 1.06 (0.67–1.67) 0.8	PS	1.27 (0.09-18.16)	0.862	1.13 (0.09-13.92)	0.923	4.22 (0.34-52.16)	0.262
malignancy (N = 89) DACT 0.74 (0.23-2.35) 0.609 0.45 (0.15-1.32) 0.144 0.45 (0.16-1.29) 0.7 PS 0.43 (0.03-5.44) 0.514 0.34 (0.03-3.76) 0.380 0.47 (0.05-4.74) 0.5 Unknown focus of infections (N = 94) 0.47 (0.17-1.28) 0.139 0.39 (0.15-1.03) 0.056 0.44 (0.17-1.14) 0.0 PS 0.09 (0.01-0.99) 0.049 0.05 (0.01-0.52) 0.013 0.03 (0.01-0.33) 0.0 Pulmonary focus of infections (N = 98) 0.89 (0.34-2.31) 0.804 0.88 (0.36-2.18) 0.782 0.68 (0.28-1.65) 0.3 DACT 0.89 (0.34-2.31) 0.804 0.88 (0.36-2.18) 0.782 0.68 (0.28-1.65) 0.3 DACT 0.89 (0.34-2.31) 0.804 0.88 (0.36-2.18) 0.782 0.68 (0.28-1.65) 0.3 DACT 0.89 (0.34-2.31) 0.804 0.88 (0.36-2.18) 0.782 0.68 (0.28-1.65) 0.3 DACT 0.89 (0.32-1.31) 0.804 0.88 (0.36-2.18) 0.75 (0.06-5.38) 0.6 DACT 0.60 (.25-1.44) 0.251 0.75 (0.32-1.76) 0.501 0.86 (0.38-1.95) <td< td=""><td>Haematological</td><td></td><td></td><td></td><td></td><td></td><td></td></td<>	Haematological						
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	malignancy ($N = 89$)						
PS 0.43 (0.03-5.44) 0.514 0.34 (0.03-3.76) 0.380 0.47 (0.05-4.74) 0.514 0.34 (0.03-3.76) 0.380 0.47 (0.05-4.74) 0.514 0.47 (0.05-4.74) 0.515 0.516 0.514 0.34 (0.03-3.76) 0.380 0.47 (0.05-4.74) 0.515 0.514 0.514 0.025 0.514 0.39 (0.15-1.03) 0.056 0.44 (0.17-1.14) 0.055 0.47 (0.05-4.74) 0.515 0	DACT	0.74 (0.23–2.35)	0.609	0.45 (0.15–1.32)	0.144	0.45 (0.16–1.29)	0.138
Unknown focus of infections (N = 94) DACT 0.47 (0.17-1.28) 0.139 0.39 (0.15-1.03) 0.056 0.44 (0.17-1.14) 0.07 PS 0.09 (0.01-0.99) 0.049 0.05 (0.01-0.52) 0.013 0.03 (0.01-0.33) 0.07 Pulmonary focus of infections (N = 98) DACT 0.89 (0.34-2.31) 0.804 0.88 (0.36-2.18) 0.782 0.68 (0.28-1.65) 0.35 PS 0.32 (0.03-3.56) 0.354 0.31 (0.03-3.11) 0.321 0.57 (0.06-5.38) 0.67 Time to blood culture positivity <7.5 h (N = 139) DACT 0.60 (.25-1.44) 0.251 0.75 (0.32-1.76) 0.501 0.86 (0.38-1.95) 0.77 PS 0.14 (0.02-0.95) 0.044 0.06 (0.01-0.44) 0.005 0.09 (0.02-0.56) 0.07 Ps 0.14 (0.02-0.70) 0.018 0.34 (0.09-1.27) 0.107 0.26 (0.08-0.92) 0.07 PS 82.18 (1.71-3952.63 0.026 6.79 (0.38-122.12) 0.194 8.79 (0.56-136.83) 0.17 Empirical active β-lactam (N = 482) DACT 0.84 (0.49-1.44) 0.528 0.85 (0.52-1.39) 0.516 1.06 (0.67-1.67) 0.88	PS	0.43 (0.03–5.44)	0.514	0.34 (0.03–3.76)	0.380	0.47 (0.05–4.74)	0.521
$\begin{array}{c ccccc} \text{infections } (N = 94) \\ \text{DACT} & 0.47 \ (0.17-1.28) & 0.139 & 0.39 \ (0.15-1.03) & 0.056 & 0.44 \ (0.17-1.14) & 0.056 \\ \text{PS} & 0.09 \ (0.01-0.99) & \textbf{0.049} & 0.05 \ (0.01-0.52) & \textbf{0.013} & 0.03 \ (0.01-0.33) & \textbf{0.016} \\ \text{Pulmonary focus of} \\ \text{infections } (N = 98) \\ \text{DACT} & 0.89 \ (0.34-2.31) & 0.804 & 0.88 \ (0.36-2.18) & 0.782 & 0.68 \ (0.28-1.65) & 0.356 \\ \text{PS} & 0.32 \ (0.03-3.56) & 0.354 & 0.31 \ (0.03-3.11) & 0.321 & 0.57 \ (0.06-5.38) & 0.66 \\ \text{Pseudomonas} \\ \begin{array}{c} \text{aeruginosa} \ (N = 61)^{\text{b}} \\ \text{DACT} & 0.12 \ (0.02-0.70) & \textbf{0.018} \\ \text{DACT} & 0.12 \ (0.02-0.70) & \textbf{0.018} \\ \text{DACT} & 0.84 \ (0.49-1.44) & 0.528 & 0.85 \ (0.52-1.39) & 0.516 & 1.06 \ (0.67-1.67) & 0.86 \\ \begin{array}{c} \text{O.67-1.67} & 0.84 \ (0.49-1.44) \\ \text{O.528} & 0.85 \ (0.52-1.39) & 0.516 & 1.06 \ (0.67-1.67) & 0.86 \\ \end{array}$	Unknown focus of						
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	infections ($N = 94$)	0 (7 (0 (7 (0 0))	0.400	0.00 (0.45.4.00)	0.055		
PS 0.09 (0.01-0.99) 0.049 0.05 (0.01-0.52) 0.013 0.03 (0.01-0.33) 0.049 0.05 (0.01-0.52) 0.013 0.03 (0.01-0.33) 0.049 0.05 (0.01-0.52) 0.013 0.03 (0.01-0.33) 0.049 0.05 (0.01-0.52) 0.013 0.03 (0.01-0.33) 0.049 0.05 (0.01-0.52) 0.013 0.03 (0.01-0.33) 0.049 0.05 0.05 (0.01-0.52)	DACI	0.47(0.17-1.28)	0.139	0.39 (0.15-1.03)	0.056	0.44(0.1/-1.14)	0.090
Pulmonary focus of infections (N = 98) DACT 0.89 (0.34–2.31) 0.804 0.88 (0.36–2.18) 0.782 0.68 (0.28–1.65) 0.57 PS 0.32 (0.03–3.56) 0.354 0.31 (0.03–3.11) 0.321 0.57 (0.06–5.38) 0.67 Time to blood culture positivity <7.5 h (N = 139) DACT 0.60 (.25–1.44) 0.251 0.75 (0.32–1.76) 0.501 0.86 (0.38–1.95) 0.77 PS 0.14 (0.02–0.95) 0.044 0.06 (0.01–0.44) 0.005 0.09 (0.02–0.56) 0.07 Ps 0.12 (0.02–0.70) 0.018 0.34 (0.09–1.27) 0.107 0.26 (0.08–0.92) 0.07 PS 82.18 (1.71–3952.63 0.026 6.79 (0.38–122.12) 0.194 8.79 (0.56–136.83) 0.17 PS 0.44 (0.49–1.44) 0.528 0.85 (0.52–1.39) 0.516 1.06 (0.67–1.67) 0.88	PS C C	0.09 (0.01-0.99)	0.049	0.05 (0.01-0.52)	0.013	0.03 (0.01-0.33)	0.004
Infections (N = 98) DACT 0.89 (0.34-2.31) 0.804 0.88 (0.36-2.18) 0.782 0.68 (0.28-1.65) 0.57 PS 0.32 (0.03-3.56) 0.354 0.31 (0.03-3.11) 0.321 0.57 (0.06-5.38) 0.67 Time to blood culture positivity <7.5 h (N = 139) DACT 0.60 (.25-1.44) 0.251 0.75 (0.32-1.76) 0.501 0.86 (0.38-1.95) 0.77 PS 0.14 (0.02-0.95) 0.044 0.06 (0.01-0.44) 0.005 0.09 (0.02-0.56) 0.07 Ps 0.12 (0.02-0.70) 0.018 0.34 (0.09-1.27) 0.107 0.26 (0.08-0.92) 0.07 PS 82.18 (1.71-3952.63 0.026 6.79 (0.38-122.12) 0.194 8.79 (0.56-136.83) 0.17 PS 0.84 (0.49-1.44) 0.528 0.85 (0.52-1.39) 0.516 1.06 (0.67-1.67) 0.88	Pulmonary focus of						
DACI $0.89 (0.34-2.31)$ 0.804 $0.88 (0.36-2.18)$ 0.782 $0.68 (0.28-1.65)$ 0.57 PS $0.32 (0.03-3.56)$ 0.354 $0.31 (0.03-3.11)$ 0.321 $0.57 (0.06-5.38)$ 0.68 Time to blood culture positivity <7.5 h (N = 139)	infections ($N = 98$)	0.00 (0.0 (0.00/		0.700		0.000
PS $0.32 (0.03-3.56)$ 0.354 $0.31 (0.03-3.11)$ 0.321 $0.57 (0.06-5.38)$ 0.67 Time to blood culture positivity <7.5 h (N = 139)	DACI	0.89 (0.34-2.31)	0.804	0.88 (0.36-2.18)	0.782	0.68 (0.28-1.65)	0.396
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	PS	0.32 (0.03-3.56)	0.354	0.31 (0.03-3.11)	0.321	0.57 (0.06-5.38)	0.625
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	lime to blood culture						
DACT $0.60(.25-1.44)$ 0.251 $0.75(0.32-1.76)$ 0.501 $0.86(0.38-1.95)$ $0.75(0.32-1.76)$ PS $0.14(0.02-0.95)$ 0.044 $0.06(0.01-0.44)$ 0.005 $0.09(0.02-0.56)$ $0.66(0.08-0.92)$ Pseudomonasaeruginosa (N = 61) ^b DACT $0.12(0.02-0.70)$ 0.018 $0.34(0.09-1.27)$ 0.107 $0.26(0.08-0.92)$ $0.66(0.08-0.92)$ PSBactrian (N = 482)DACT $0.84(0.49-1.44)$ 0.528 $0.85(0.52-1.39)$ 0.516 $1.06(0.67-1.67)$ $0.88(0.67-1.67)$	positivity < 7.5 h ($N = 139$)		0.051		0.501	0.00 (0.20, 1.05)	0 717
PS $0.14 (0.02-0.95)$ 0.044 $0.06 (0.01-0.44)$ 0.005 $0.09 (0.02-0.56)$ 0.018 Pseudomonas $aeruginosa (N = 61)^b$ $0.12 (0.02-0.70)$ 0.018 $0.34 (0.09-1.27)$ 0.107 $0.26 (0.08-0.92)$ 0.026 PS $82.18 (1.71-3952.63)$ 0.026 $6.79 (0.38-122.12)$ 0.194 $8.79 (0.56-136.83)$ 0.31 DACT $0.84 (0.49-1.44)$ 0.528 $0.85 (0.52-1.39)$ 0.516 $1.06 (0.67-1.67)$ 0.88	DACI	0.60 (.25-1.44)	0.251	0.75(0.32 - 1.76)	0.501	0.86 (0.38-1.95)	0./1/
$\begin{array}{c} \text{Act} \\ \text{Ps} \\ \text{Empirical active} \\ \beta-\text{lactarn} (N=482) \\ \text{DACT} \\ \text{OACT} \\ \text{DACT} \\ \text{OACT} \\ \text{OACH} \\ \text{OACT} \\ \text{OACH} \\ \text{OACT} \\ \text{OACH} \\ \text{OACH}$	PS Decudementes	0.14 (0.02-0.95)	0.044	0.06 (0.01-0.44)	0.005	0.09 (0.02-0.56)	0.010
$\begin{array}{c} \text{DACT} & 0.12 \ (0.02-0.70) & \textbf{0.018} & 0.34 \ (0.09-1.27) & 0.107 & 0.26 \ (0.08-0.92) & \textbf{0.018} \\ \text{PS} & 82.18 \ (1.71-3952.63) & \textbf{0.026} & 6.79 \ (0.38-122.12) & 0.194 & 8.79 \ (0.56-136.83) & 0.128 \\ \text{Empirical active} \\ \beta-\text{lactam} \ (N=482) \\ \text{DACT} & 0.84 \ (0.49-1.44) & 0.528 & 0.85 \ (0.52-1.39) & 0.516 & 1.06 \ (0.67-1.67) & 0.88 \\ \end{array}$	Pseudomonas						
DACT 0.12 (0.02-0.70) 0.016 0.34 (0.09-1.27) 0.107 0.26 (0.08-0.92) 0.44 PS 82.18 (1.71-3952.63) 0.026 6.79 (0.38-122.12) 0.194 8.79 (0.56-136.83) 0.12 B-lactam (N = 482) DACT 0.84 (0.49-1.44) 0.528 0.85 (0.52-1.39) 0.516 1.06 (0.67-1.67) 0.84	$deruginosa (N = 61)^{-1}$	0 12 (0 02 0 70)	0.018	0.24 (0.00, 1.27)	0 1 0 7	0.26 (0.08, 0.02)	0.036
P3 $82.16 (1.71-3932.03)$ 0.028 $0.79 (0.38-122.12)$ 0.194 $0.79 (0.36-136.83)$ 0.194 Empirical active β-lactam (N = 482) DACT $0.84 (0.49-1.44)$ 0.528 $0.85 (0.52-1.39)$ 0.516 $1.06 (0.67-1.67)$ $0.84 (0.49-1.44)$		0.12 (0.02-0.70)	0.018	0.54 (0.09-1.27)	0.107	0.20 (0.06-0.92)	0.030
$\begin{array}{c} \beta - lactam (N = 482) \\ DACT & 0.84 (0.49 - 1.44) & 0.528 & 0.85 (0.52 - 1.39) & 0.516 & 1.06 (0.67 - 1.67) & 0.88 \\ \end{array}$	P3	02.10 (1.71-5952.05)	0.020	0.79 (0.36-122.12)	0.194	0.79 (0.30-130.03)	0.121
DACT 0.84 (0.49–1.44) 0.528 0.85 (0.52–1.39) 0.516 1.06 (0.67–1.67) 0.8	$\beta_{\rm lactary}(N = 482)$						
	p-lucturi ($N = 402$)	0.8/ (0.49-1.4/4)	0 5 2 8	0.85 (0.52-1.30)	0.516	1.06 (0.67-1.67)	0.820
	DACI	0.63 (0.45-1.44)	0.520	0.63(0.32 - 1.33) 0.63(0.22 - 1.81)	0.310	0.56(0.07 - 1.07)	0.620



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Clinica Malattie Infettive Ospedale Policlinico San Martino IRCCS Ripa M et al - J Antimicrob Chemother doi: 10.1093/jac/dkx







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Focus on: Pseudomonas aeruginosa BSI

- **Background:** Empirical COMBO is often recommended for pts with known or suspected *P.aeruginosa* septic shock to ensure antibiotic susceptibility and reduce R development.
- Gap in knowledge: there's limited and conflicting data on its synergistic effects, especially in septic shock patients who are at high risk of adverse outcomes.
- Study population: all consecutive patients with septic shock due to *P.aeruginosa* BSI. We compared the outcomes of patients receiving adequate empirical combination therapy (AECT) to those on adequate empirical monotherapy (AEMT).
- 98 patients with septic shock treated with adequate therapy 24 received AECT vd 74: AEMT



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	Total	AEMT	AECT	Divalua
VARIABLE	N=98	(n = 74)	(n = 24)	P-value
Age (years), median (IQR)	68.0 (58.0-76.0)	70.0 (59.8-78.0)	60 (49.8-69.7)	0.006
Male sex, n (%)	63 (64.3)	46 (62.2)	17 (70.8)	0.48
Underlying diseases, n (%)				
Cardiovascular disease	33 (33.7)	26 (35.1)	7 (29.2)	0.63
Solid malignancy	24 (24.5)	18 (24.3)	6 (25.0)	1.00
Neurological disease	23 (23.5)	19 (25.7)	4 (16.7)	0.42
Diabetes mellitus	17 (17.3)	15 (20.3)	2 (8.3)	0.23
Chronic obstructive pulmonary disease	14 (14.3)	12 (16.2)	2 (8.3)	0.51
Gastrointestinal disease	13 (13.3)	7 (9.5)	6 (25.0)	0.08
Neutropenia, n (%)	10 (10.2)	5 (6.8)	5 (20.8)	0.06
Invasive procedures #, n (%)				
Urinary catheter	66 (67.3)	50 (67.6)	16 (66.7)	1.00
Central venous catheters	63 (64.3)	47 (63.5)	16 (66.7)	1.00
Any surgery	32 (32.7)	26 (35.1)	6 (25.0)	0.46
Susceptibility profile, n (%)*				
Non-MDR	90 (91.8)	71 (95.9)	19 (79.2)	0.01
MDR-XDR*	8 (8.2)	3 (4.1)	5 (20.8)	0.01
Low-risk BSI, n (%)	25 (25.5)	19 (25.7)	6 (25.0)	0.46
Central venous catheter-associated BSI	17 (17.3)	11 (14.9)	6 (25.0)	0.35
Skin and soft tissue infection	5 (5.1)	5 (6.8)	0 (0.0)	0.33
Urinary tract	3 (3.1)	3 (4.1)	0 (0.0)	1.00
High-risk BSI, n (%)	73 (74.5)	55 (74.3)	18 (75.0)	1.00
Respiratory tract	35 (35.7)	25 (33.8)	10 (41.7)	0.63
Primary origin	32 (32.7)	27 (36.5)	5 (20.8)	0.21
Abdominal	6 (6.1)	3 (4.1)	3 (12.5)	0.16

Pseudomonas aeruginosa BSI

30-day all-cause mortality rate: 49.0% (48/98) **Mortality:** AECT group 25.0% (6/24) vs 56.8% (42/74) p= 0.01.

Multivariable analysis for 30 day mortality			
Variable	aHR	IC95%	Р
Age, years	1.01	0.99-1.04	0.22
Adequate empirical combination therapy	0.39	0.16-0.95	0.04
High risk source bloodstream infection	2.60	1.16-5.82	0.02



Conclusions

- Adequate empirical combination therapy can decrease 30-day all-cause mortality in patient with septic shock caused by P. aeruginosa BSI
- **From a clinical point of view:** The selection of AECT should consider individual patient risks, prior history of colonization, and the local epidemiology. We postulate that novel antibiotics, such as ceftolozane-tazobactam, ceftazidime-avibactam, imipenem-relebactam and cefiderocol, when combined with aminoglycosides or fosfomycin, may offer a promising approach. Further studies are needed..



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Rationale for combination therapy in *P.aeruginosa* infections

- Increase the probability of adequate empirical therapy? Maybe yes but promptly tailor abx based on AST
- In vivo synergistic activity that might improve clinical outcome? No clear benefit
- Prevent development of resistance?
 Similar to HIV or TB
 - No evidence for MDR-GNB (consider all the microbioma; Not only the isolated strain!)



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3- Do not forget the source control....



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In XDR infection control of the source is key



Falcone et al CMI 2016; 22:444



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3- Contro



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Contro













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Should we use combo or monotherapy for treating *P.aeruginosa* infections?

- Maybe YES as empirical therapy, especially for patients at high risk for MDR strains or those with septic shock.
 - Choose adequate companion according to epidemiological background and site of the infection.
- Treatment should be tailored with a single *in vitro* agent as soon as in vitro susceptibility results are available.
- Do not forget disvantages (cost, toxicity, resistance and interactions!)