LA TERAPIA DI COMBINAZIONE ANTIBATTERICA: PRO E CONTRO

Le infezioni da *Pseudomonas aeruginosa*

Antonio Vena
Infectious Diseases Clinic
University of Genoa and San Martino-IST University Hospital
Genova, Italy

UNIVERSITÀ DEGLI STUDI DI GENOVA

IRCCS Azienda Ospedaliera Universitaria San Martino – IST
Istituto Nazionale per la Ricerca sul Cancro

Disclosures
(past 5 years)

Advisor/consultant/speaker bureau

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

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

1- Concepts of *Pseudomonas aeruginosa*

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Pseudomonas aeruginosa

General concept

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

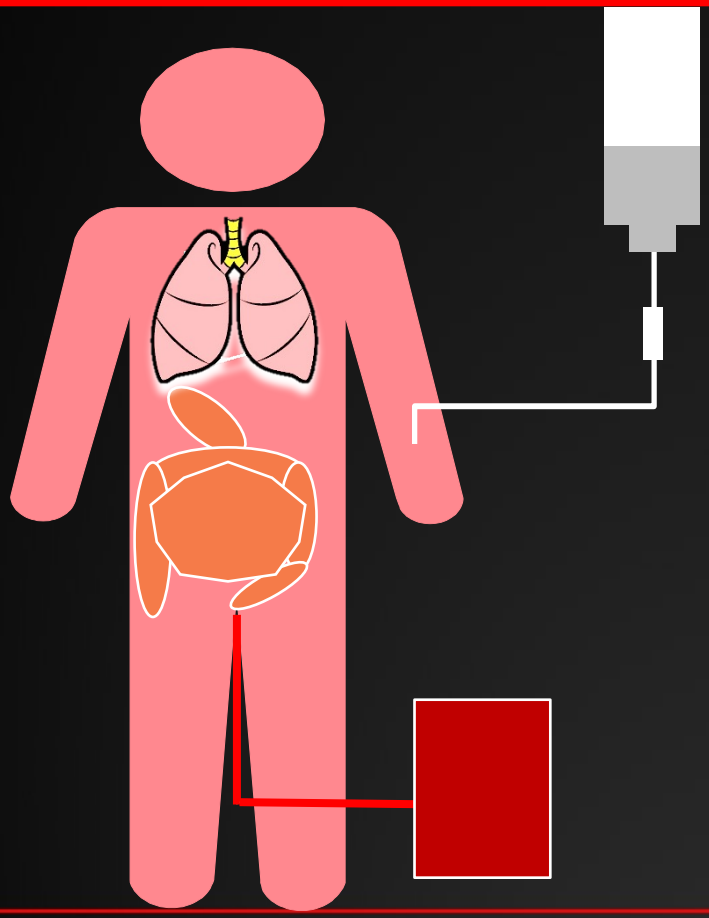
First cause of VAP and burn wound infections: *P.aeruginosa* is associated with very high mortality rates

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

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Pseudomonas aeruginosa infections



- VAP
- BSI
- Wound/Burn infections
- UTIs Related to bladder catheter
- Peritonitis (tertiary>>> secondary)

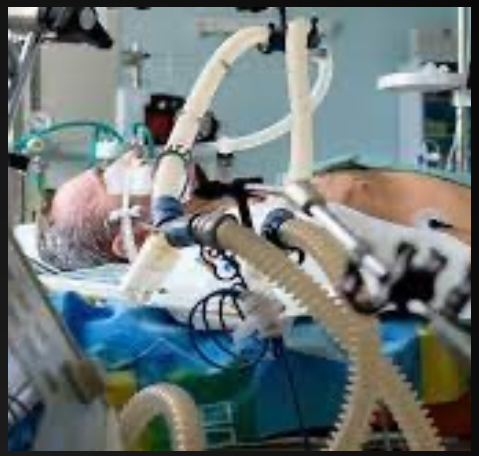
Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

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
Cumulative fluid balance[b] (per liter increase)	1.1 (1.0–1.1)	.001
Age (per year increase)	1.0 (1.0–1.0)	.001
Initial SOFA score (per point increase)	1.1 (1.0–1.1)	.002
Blood stream infection	1.7 (1.2–2.4)	.004
Cirrhosis	2.4 (1.3–4.5)	.008
Pseudomonas infection	1.6 (1.1–2.4)	.017
Medical admission	1.4 (1.0–1.8)	.049
Female gender	1.4 (1.0–1.8)	.044

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

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Rationale for combination therapy in *P.aeruginosa* infections

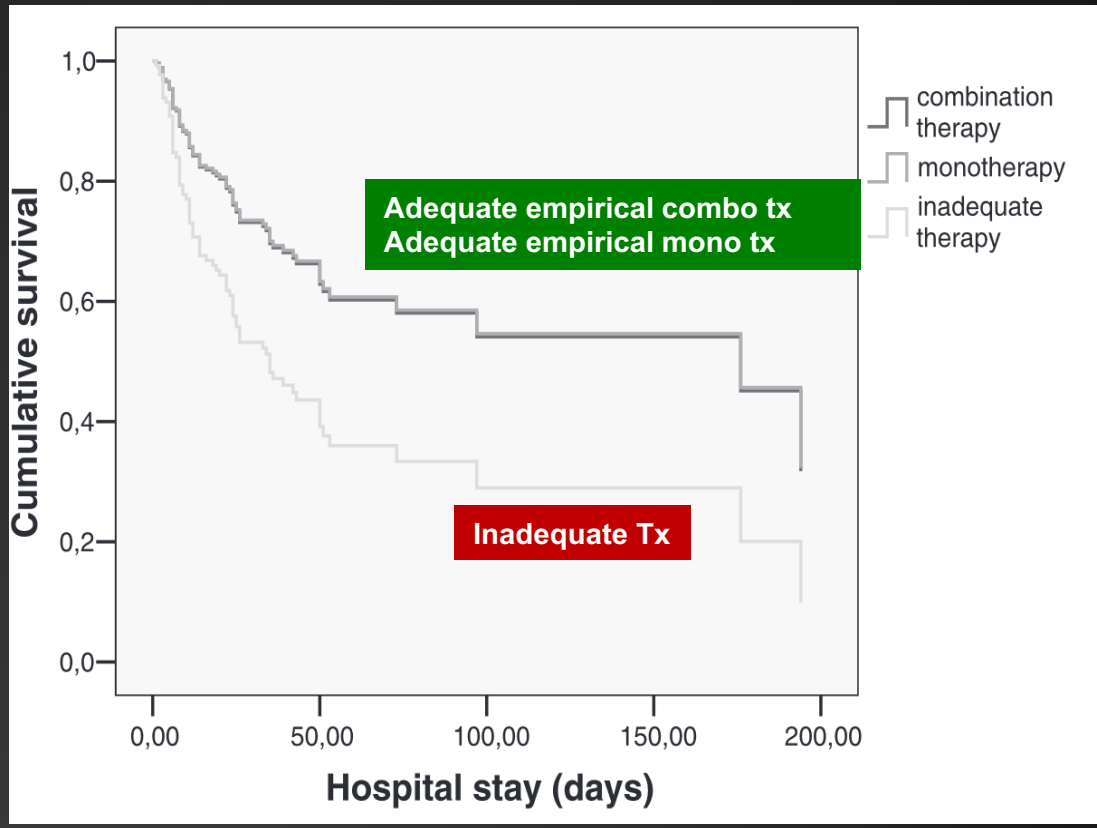
- **Increase the probability of adequate empirical therapy?**

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

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

- 183 episodes of monomicrobial *P.aeruginosa* VAP
- **Empirical therapy:** 63.3% combo vs 36.6% Mono
- **Adequate empirical therapy:** 105/116 (90.5%) **combo** vs 28/67 (56.7%) **mono**, ***p<0.001.***



Garnacho-Montero et al. Crit Care Med 2007

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

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**

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Combination therapy: when?

Empiric

- HAP / VAP / septic shock
- 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

Targeted

- *P. aeruginosa: Only in empiric initial treatment*
- *A. baumannii?*
- *K. pneumoniae (KPC)*

Bassetti M, Righi E. *Curr Opin Crit Care*. 2015 ;21(5):402-11.

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?**

β

YES
(at any)

NO (to all)

BACKBONE DRUG
Ceftolozane- tazobactam > ceftazidime-avibactam> meropenem> piperacillin-tazovactam/ ceftazidime/ cefepime

PLUS

SECOND ANTI-PSEUDOMONAL AGENT
Aminoglycoside/ colistin/ fosfomycin> fluoroquinolones

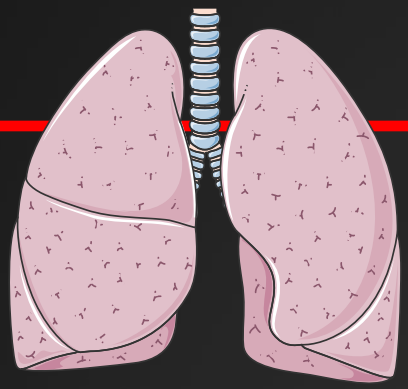
BACKBONE DRUG
Piperacillin/tazobactam/ carbapenem (maily meropenem)/ ceftazidime/ cefepime

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

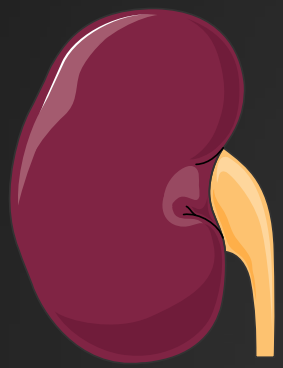
Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

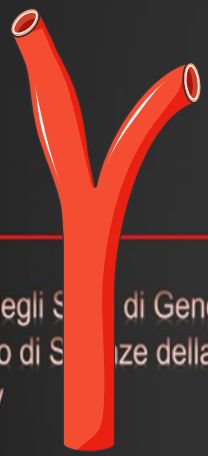
ANTI-PSEUDOMONAL BETA-LACTAM



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



+ Aminoglycoside
or colistin or
fosfomycin



+ Aminoglycoside
or colistin

Università degli S di Genova
Dipartimento di S ze della Salute (DISSAL)
Genoa, Italy

Ospedale Policlinico San Martino IRCCS
Genoa, Italy

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?**

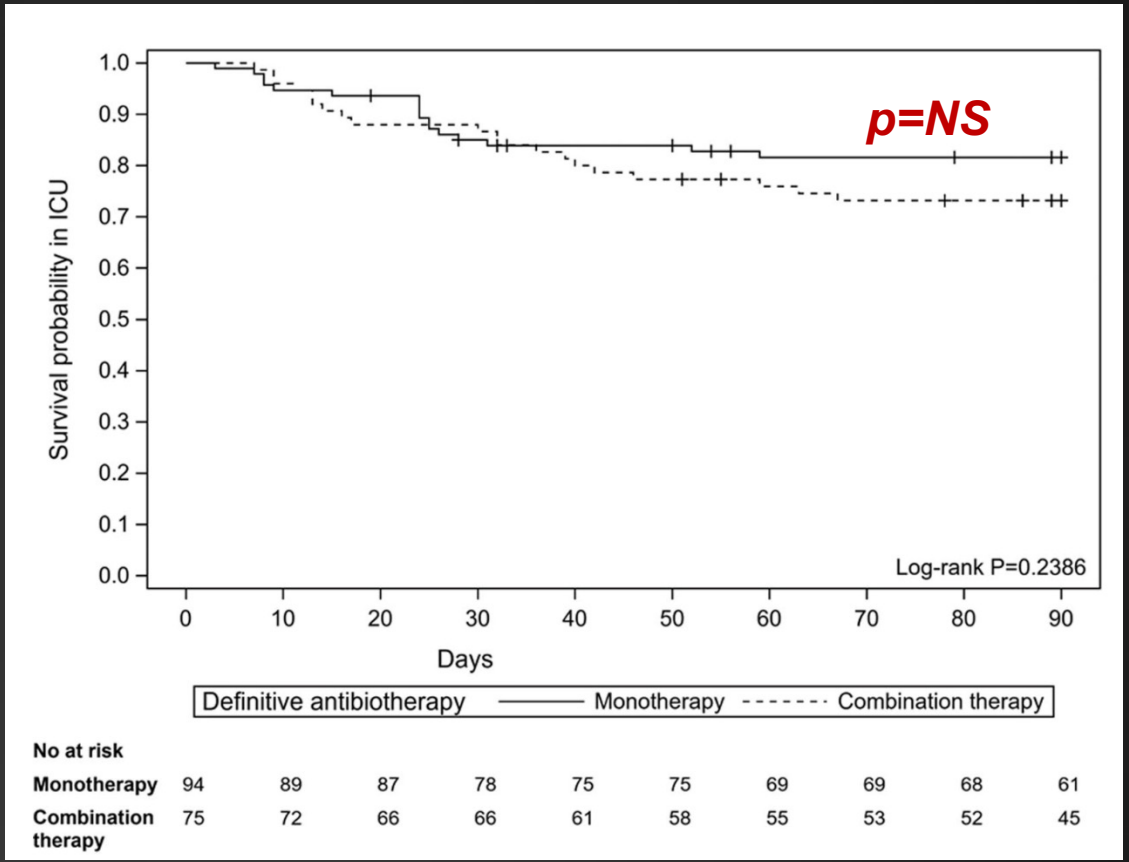
Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

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)
- **No differences** between groups in terms of other patient-centered outcomes *recurrence* of VAP and *development of MDR pathogens*



Foucrier A; Crit Care 2023

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

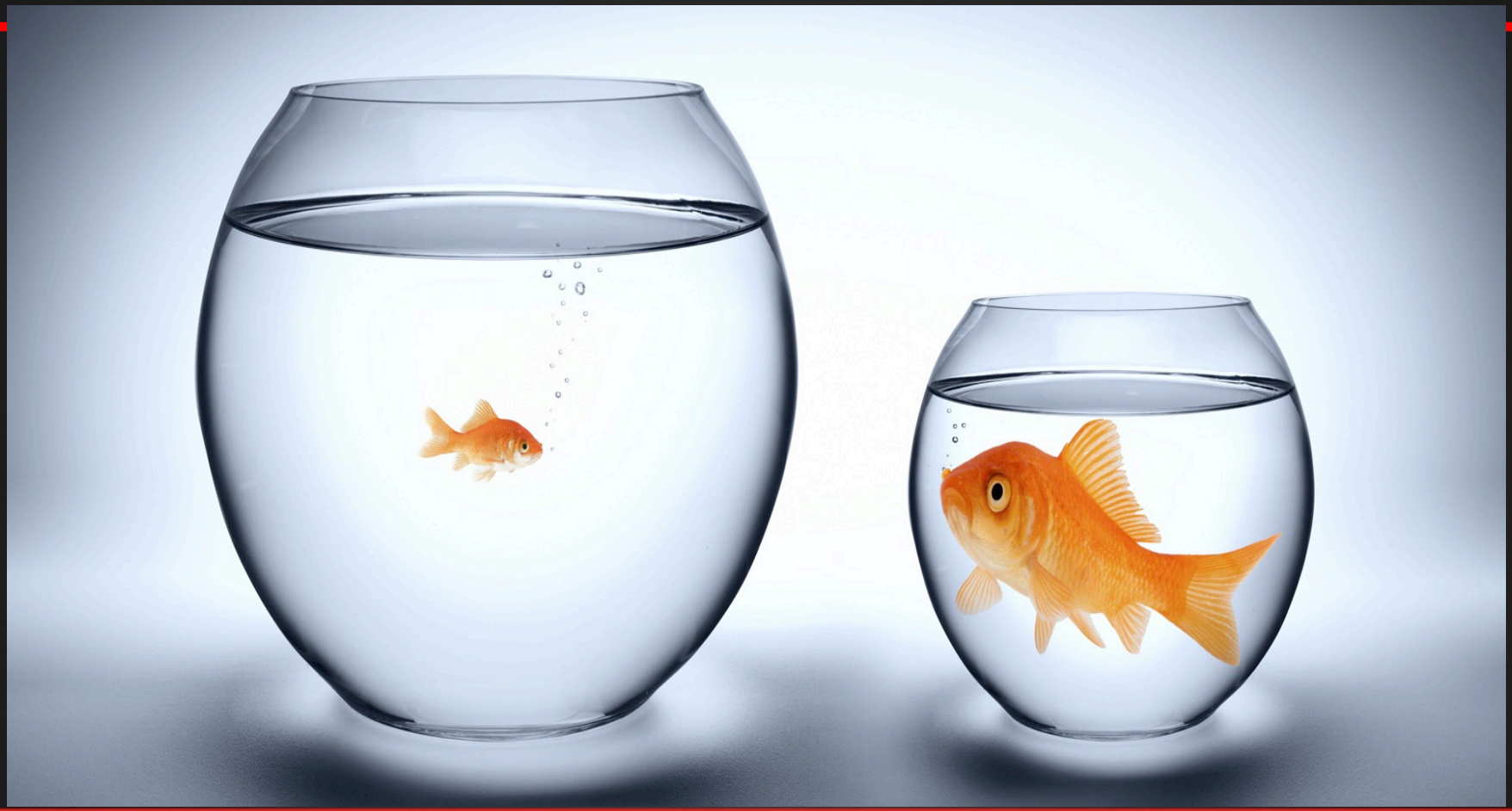
Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

Single vs double active combination (DACT) in septic shock

Table 5. PS-adjusted OR (95% CI) of the association of DACT with 7, 15 and 30 day mortality in specific subgroups

	7 day mortality		15 day mortality		30 day mortality	
Subgroup	adjusted OR (95% CI)	*P* value	adjusted OR (95% CI)	*P* value	adjusted OR (95% CI)	*P* value
Neutropenia ($N = 69$)[a]						
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**
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
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)	0.138
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
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)	0.090
PS	0.09 (0.01–0.99)	**0.049**	0.05 (0.01–0.52)	**0.013**	0.03 (0.01–0.33)	**0.004**
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)	0.396
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
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)	0.717
PS	0.14 (0.02–0.95)	**0.044**	0.06 (0.01–0.44)	**0.005**	0.09 (0.02–0.56)	**0.010**
Pseudomonas aeruginosa ($N = 61$)[b]						
DACT	0.12 (0.02–0.70)	**0.018**	0.34 (0.09–1.27)	0.107	0.26 (0.08–0.92)	**0.036**
PS	82.18 (1.71–3952.63)	**0.026**	6.79 (0.38–122.12)	0.194	8.79 (0.56–136.83)	0.121
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)	0.820
PS	0.63 (0.20–1.95)	0.422	0.63 (0.22–1.81)	0.396	0.56 (0.21–1.49)	0.246

Ripa M et al - J Antimicrob Chemother doi:10.1093/jac/dkx315- online Aug 31st 2017



Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

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**

VARIABLE	Total N=98	AEMT (n = 74)	AECT (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)	
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

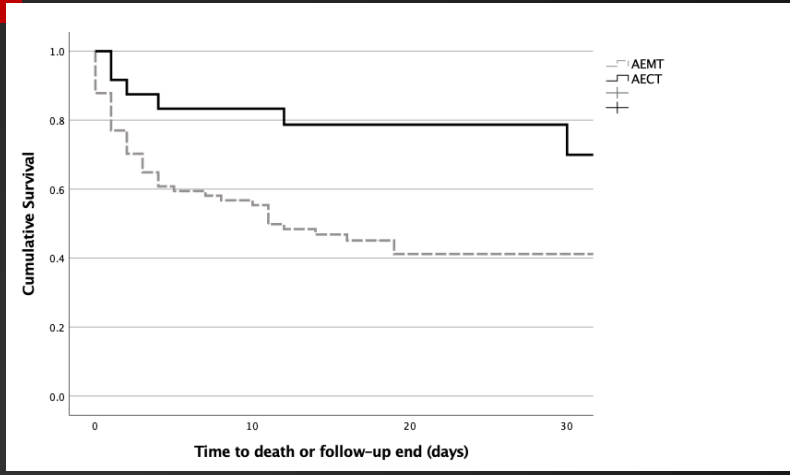
Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

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%**	P
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..*

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

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**

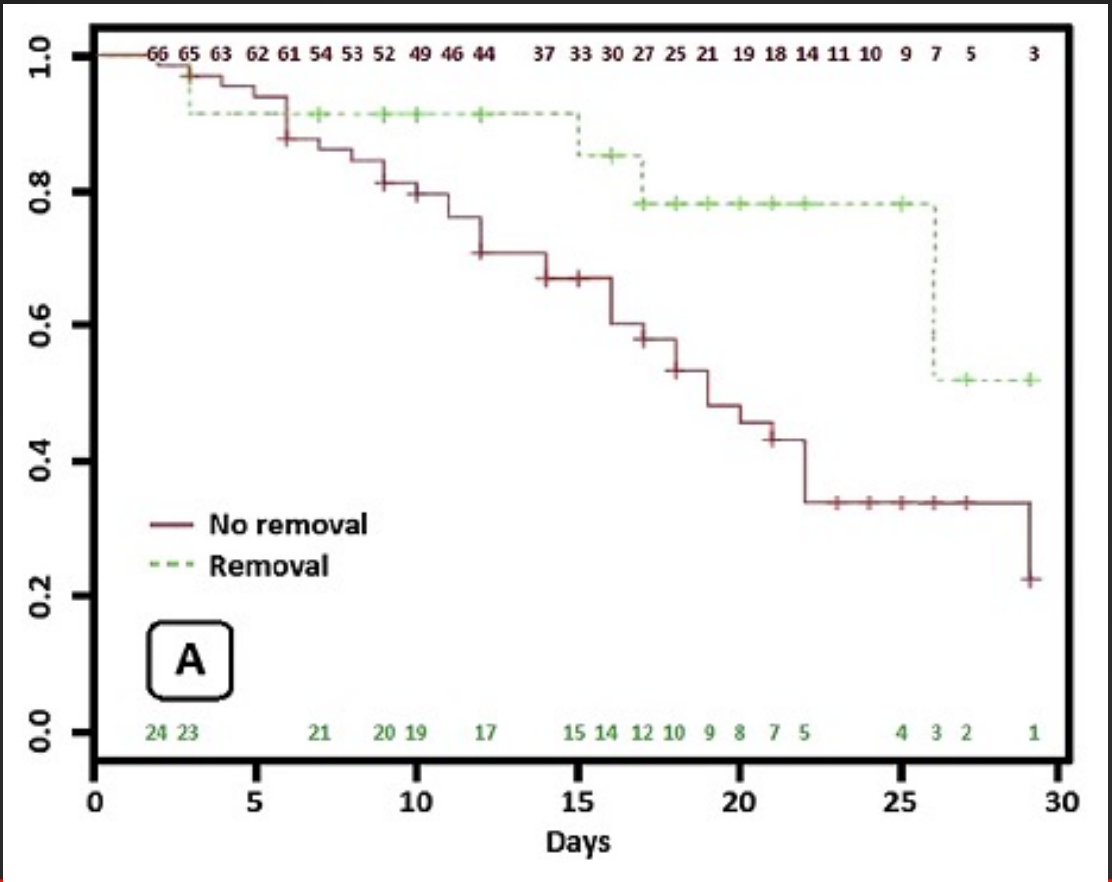
- **Prevent development of resistance?**
  - **Similar to HIV or TB**
  - **No evidence for MDR-GNB** (consider all the microbioma; Not only the isolated strain!)

Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

3- Do not forget the source control….

In XDR infection control of the source is key



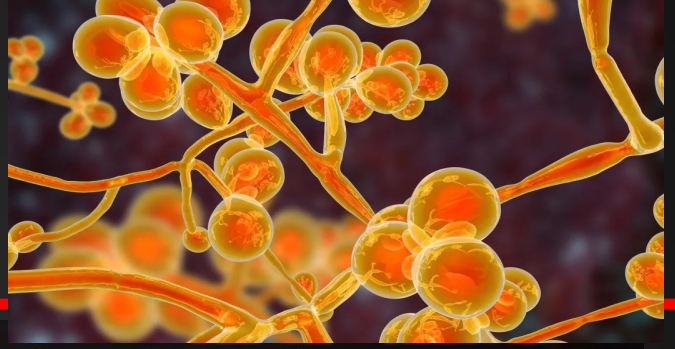
Falcone et al CMI 2016; 22:444

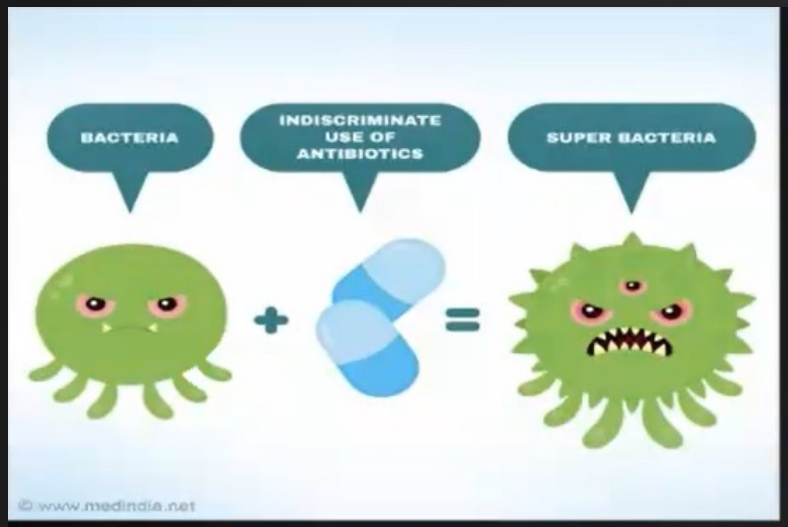
Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

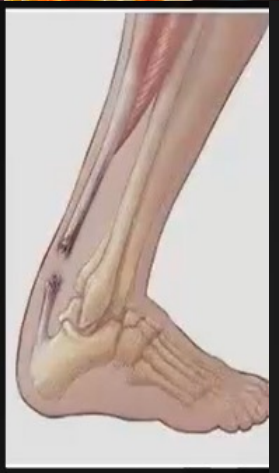
Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

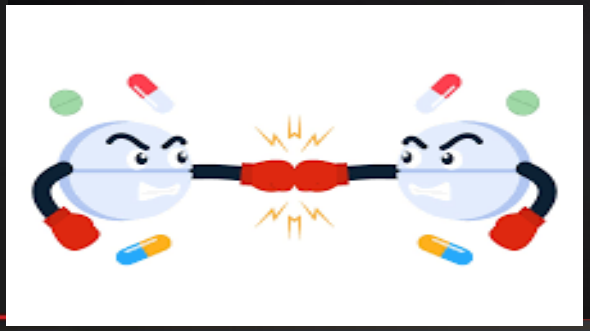
3- Contro

Contro









Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

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!)**