# Infezioni e terapia da *Pseudomonas* MDR


## Antonio Vena, MD, PhD

**Department of Health Sciences, Infectious Disease Clinic, University of Genoa, Italy.**



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

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

# 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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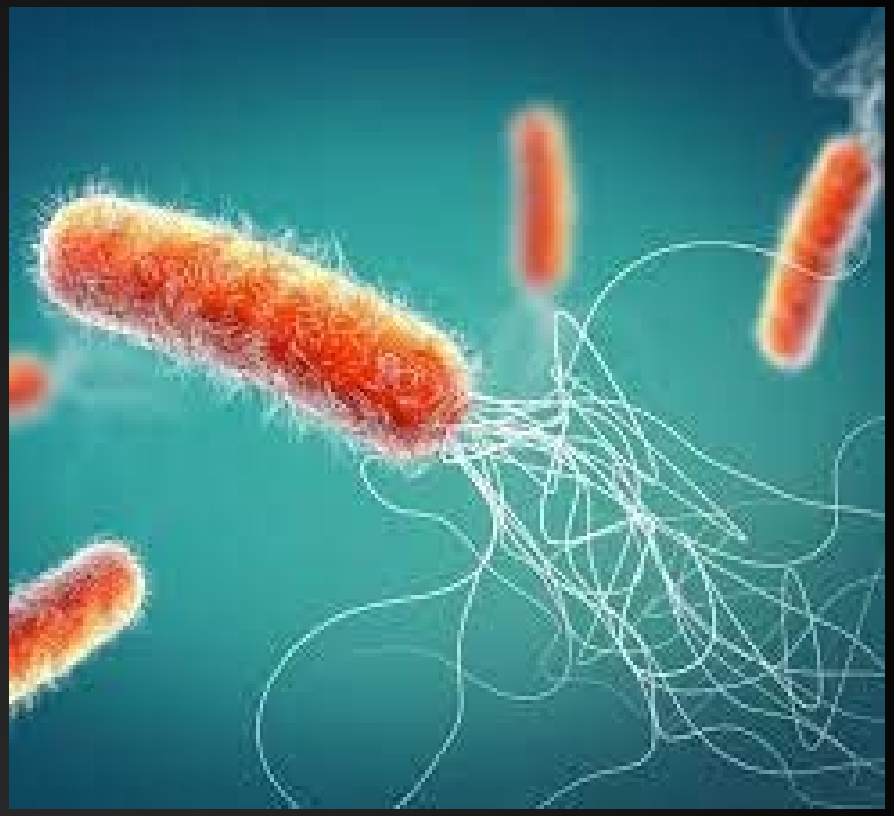
# *Pseudomonas aeruginosa*

- Gram-negative non-fermentative bacillus
- Common in the environment, (water, even contaminating distilled water)
- it is also an important cause of infections associated with hot tubs and contaminated contact lens solutions



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# *Pseudomonas aeruginosa*

## *General concept*

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. **<u>Extraordinary capacity for developing resistance</u>**

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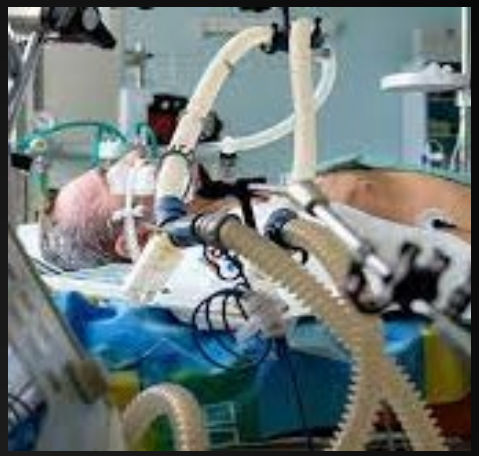
# Sepsis in European intensive care units: Results of the SOAP study

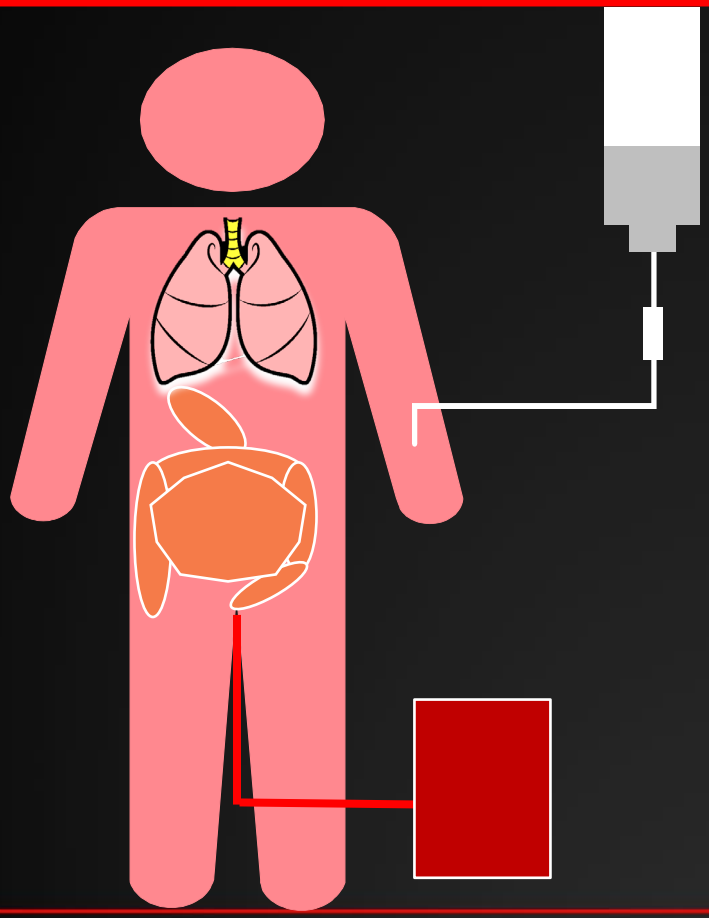
Vincent JL Critical care Medicine 2006

- 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 |
| 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 |

# *Pseudomonas aeruginosa* infections



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

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# 2- Antibiotic resistant *P.aeruginosa* in our enviroment

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# Molecular Epidemiology of *P aeruginosa aeruginosa*

| Mechanism | Characteristics |
|---|---|
| AmpC β-lactamase | ▪ Most common β-lactamase produced in *P. aeruginosa*<br>▪ Resistance to penicillins, cephalosporins (not cefepime) |
| Extended-spectrum β-lactamase | ▪ OXA: resistance to penicillins, cephalosporins, aztreonam |
| Metallo-β-lactamases | ▪ VIM, IMP, NDM: resistance to penicillins, cephalosporins, carbapenems<br>▪ Does NOT hydrolyze aztreonam |
| MexAB-OprM upregulation **(efflux pump)** | ▪ Reduced susceptibility to meropenem (NOT imipenem); reduced susceptibility or resistance to penicillins; resistance to fluoroquinolones, cephalosporins |
| OprD downregulation **(porin mutation)** | ▪ Major contributor to carbapenem resistance (eg, imipenem, reduced susceptibility to meropenem) |
| Mutations | ▪ Topoisomerase II/IV: fluoroquinolone resistance |

Any of the above can co-occur with other resistance mechanisms

Livermore. Clin Infect Dis. 2002; Xu. Infect Drug Resist. 2020

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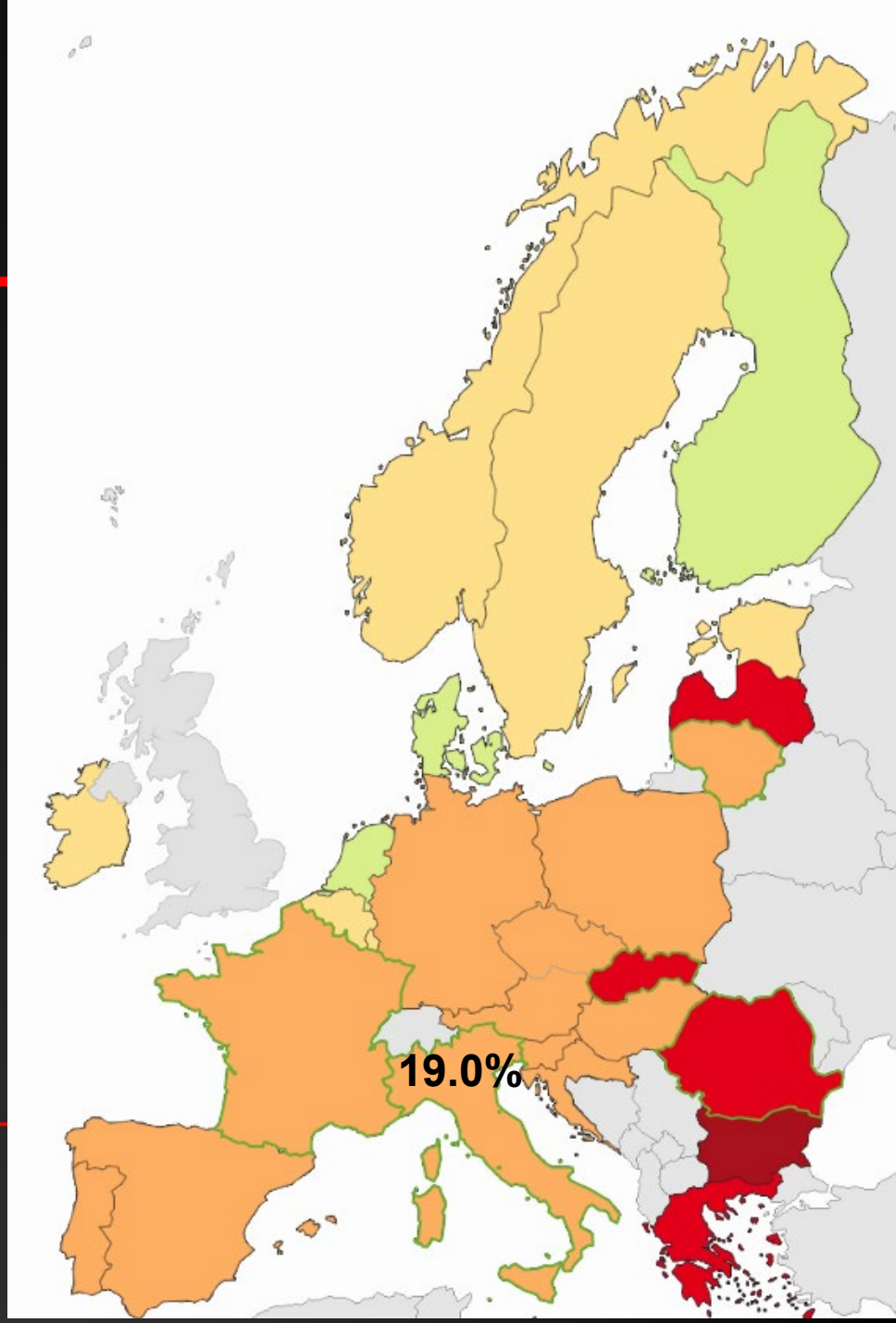
# *Pseudomonas* in E.U.
# R to 3° cefalo

**Mean European countries**
**21%**

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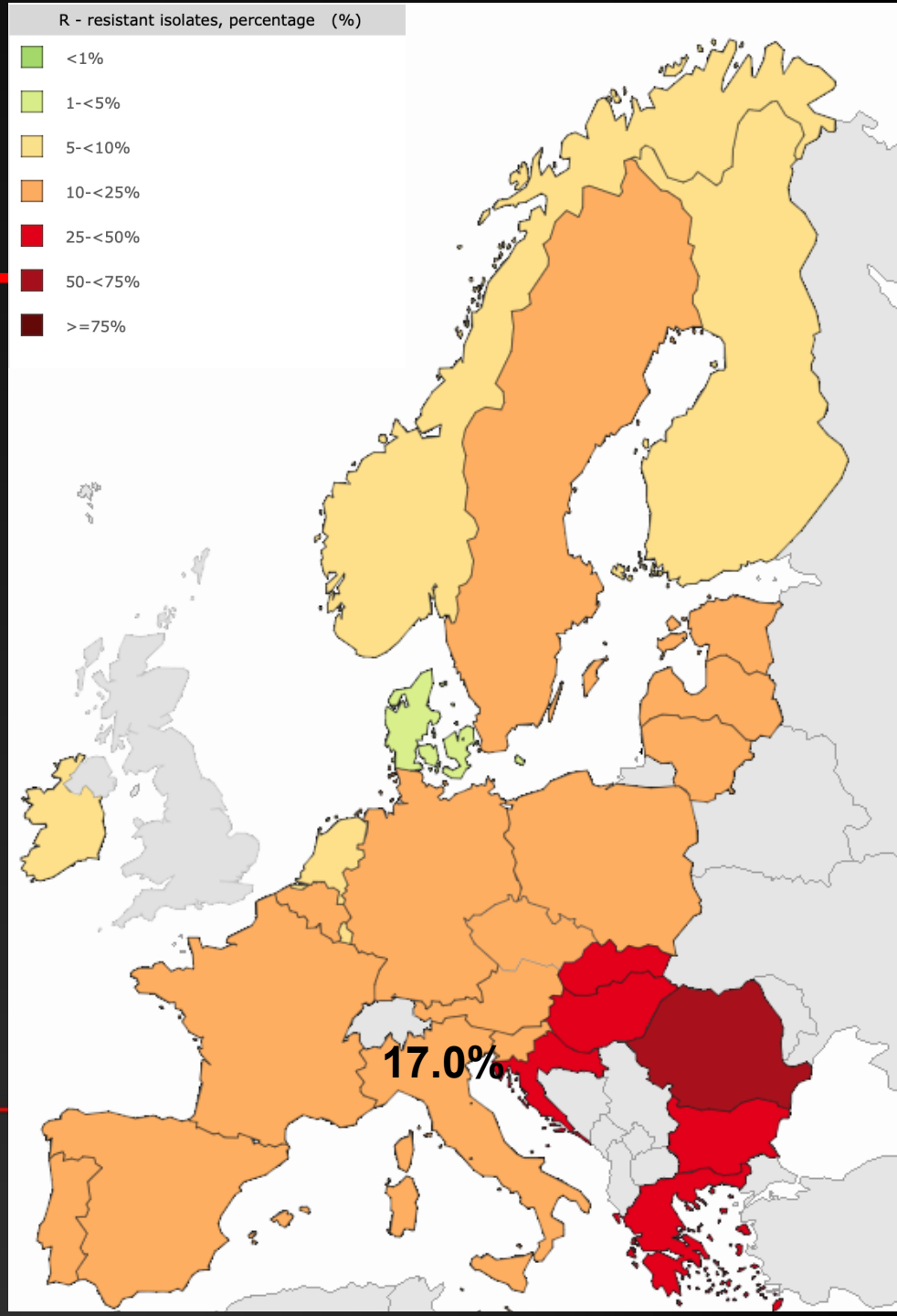
# *Pseudomonas* in E.U.
# R to carbapenems

**Mean European countries**
**19%**

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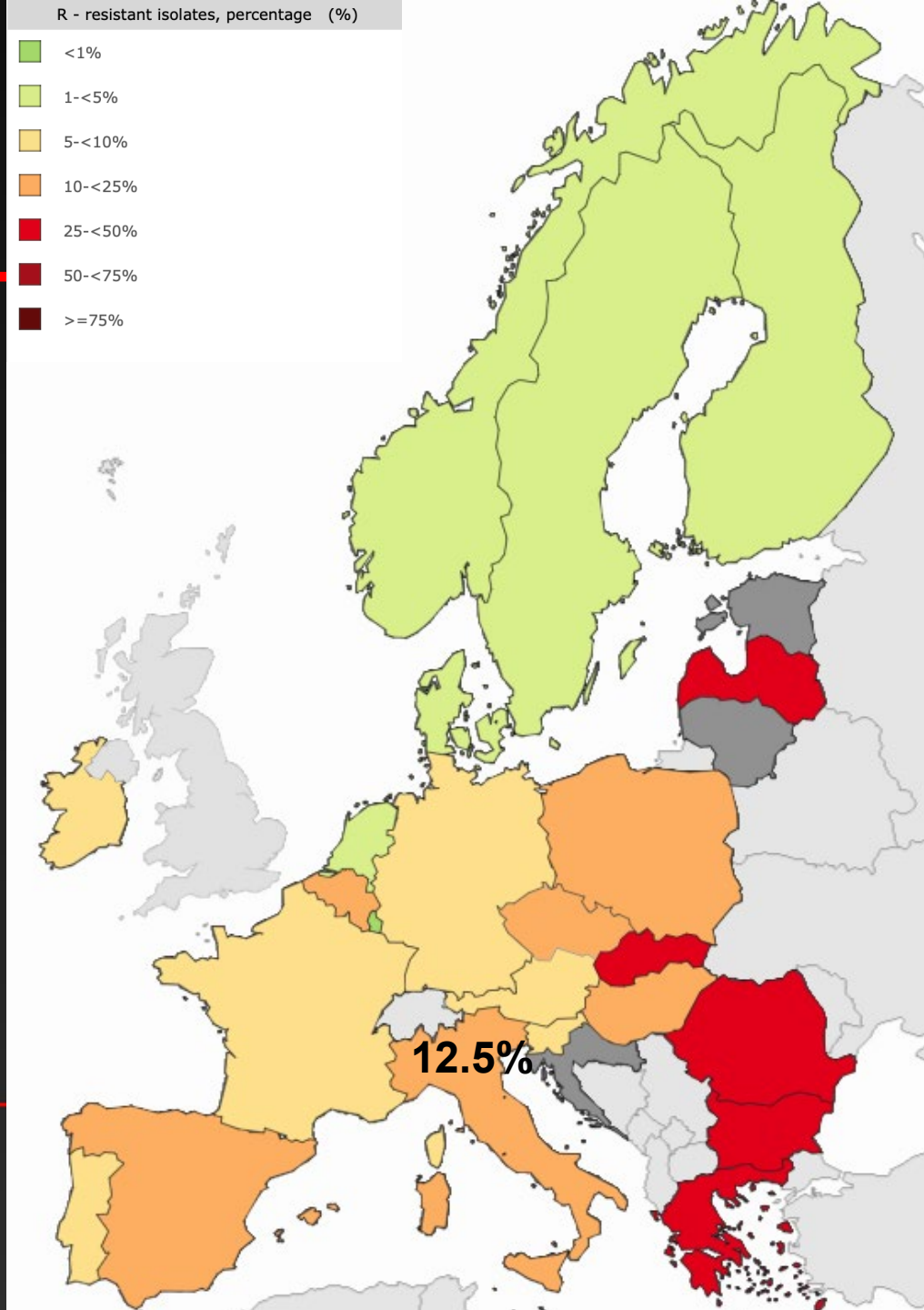
# *Pseudomonas* in E.U.

## R to MDR (R to FQs + AgIx + carba)

**Mean European countries 15%**

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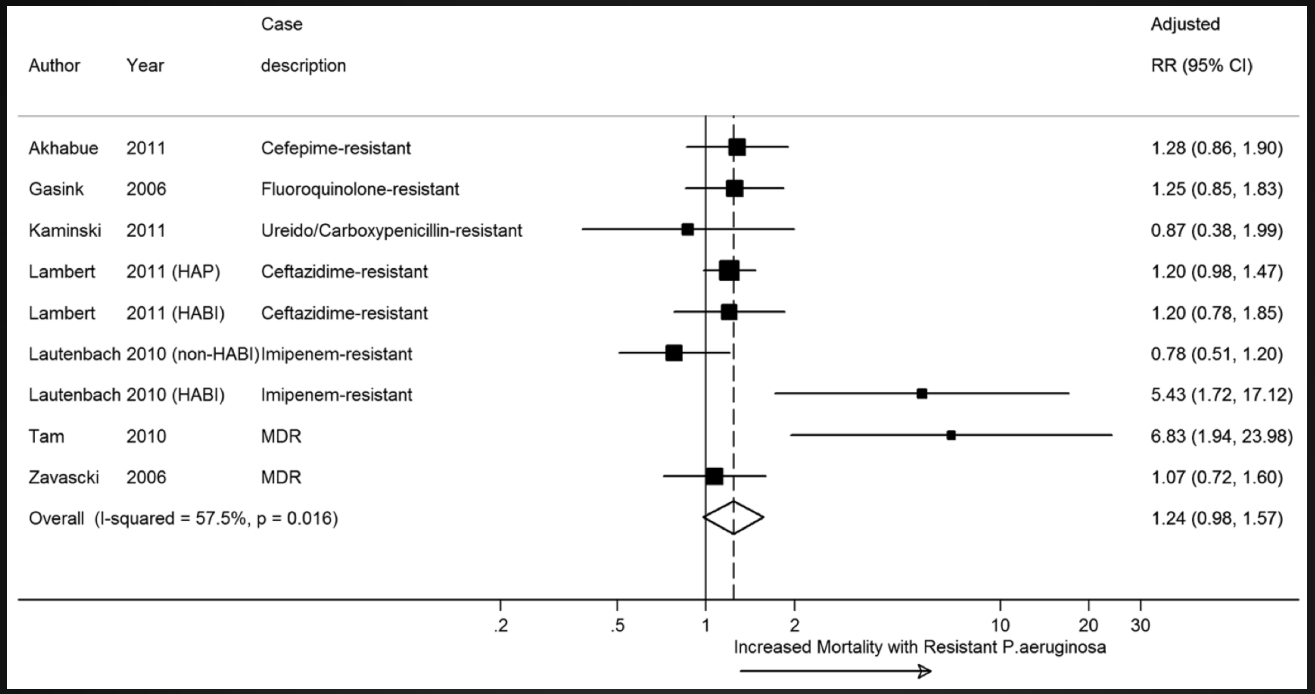
# MDR *P. aeruginosa* is associated with an increased mortality

- Systematic review:
- All-cause mortality was 34% for any resistant and 22% for susceptible *P. aeruginosa*
- MDR *P. aeruginosa* had a **>two-fold** increased risk of mortality (RR 2.34)




Nathwani D, et al. Antimicrob Resist Infect Control 2014:3:32.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# WHO list of priority multidrug resistant bacteria

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

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

**Other priority bacteria**

Priority 1: critical

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

Priority 2: high

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

Priority 3: medium

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

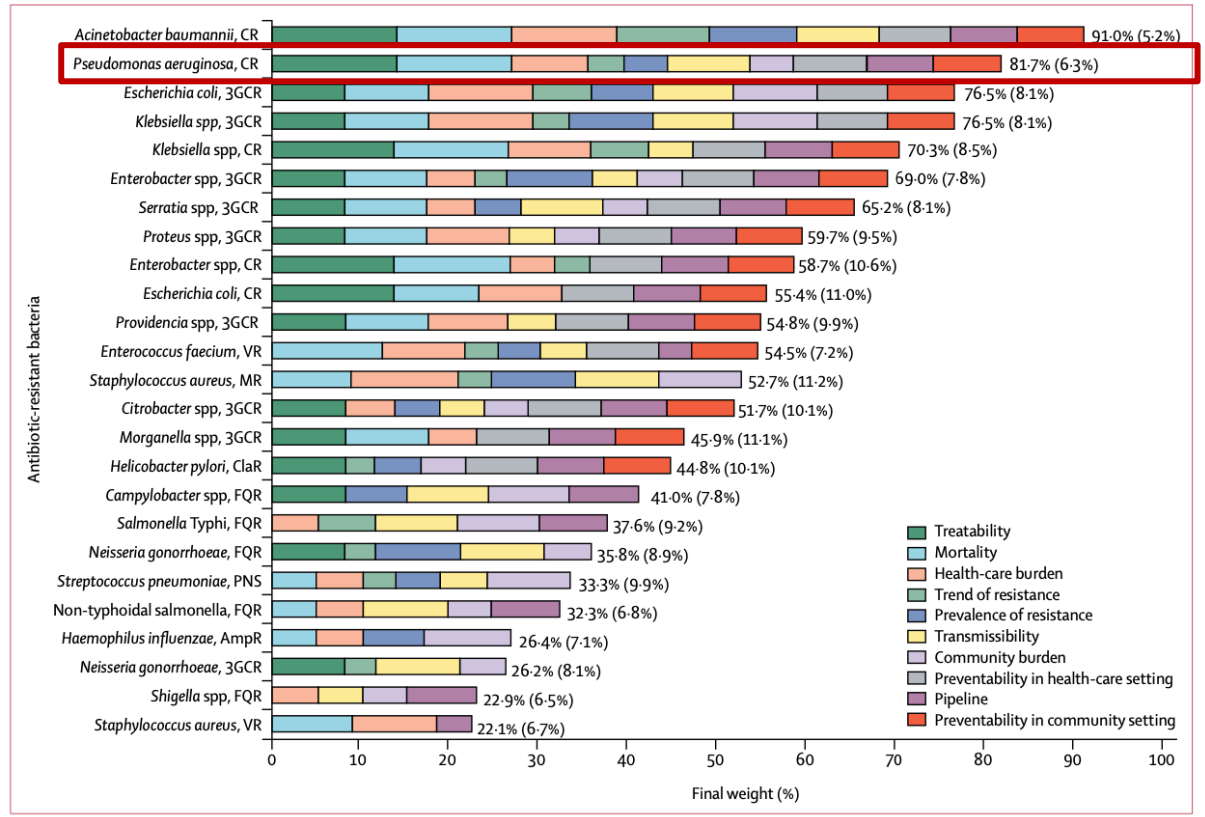


***Figure 2:*** **Final ranking of antibiotic-resistant bacteria**

Taconelli et al. Lancet Infect Dis 2018; 18:318-327


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# 3- Old antibiotics

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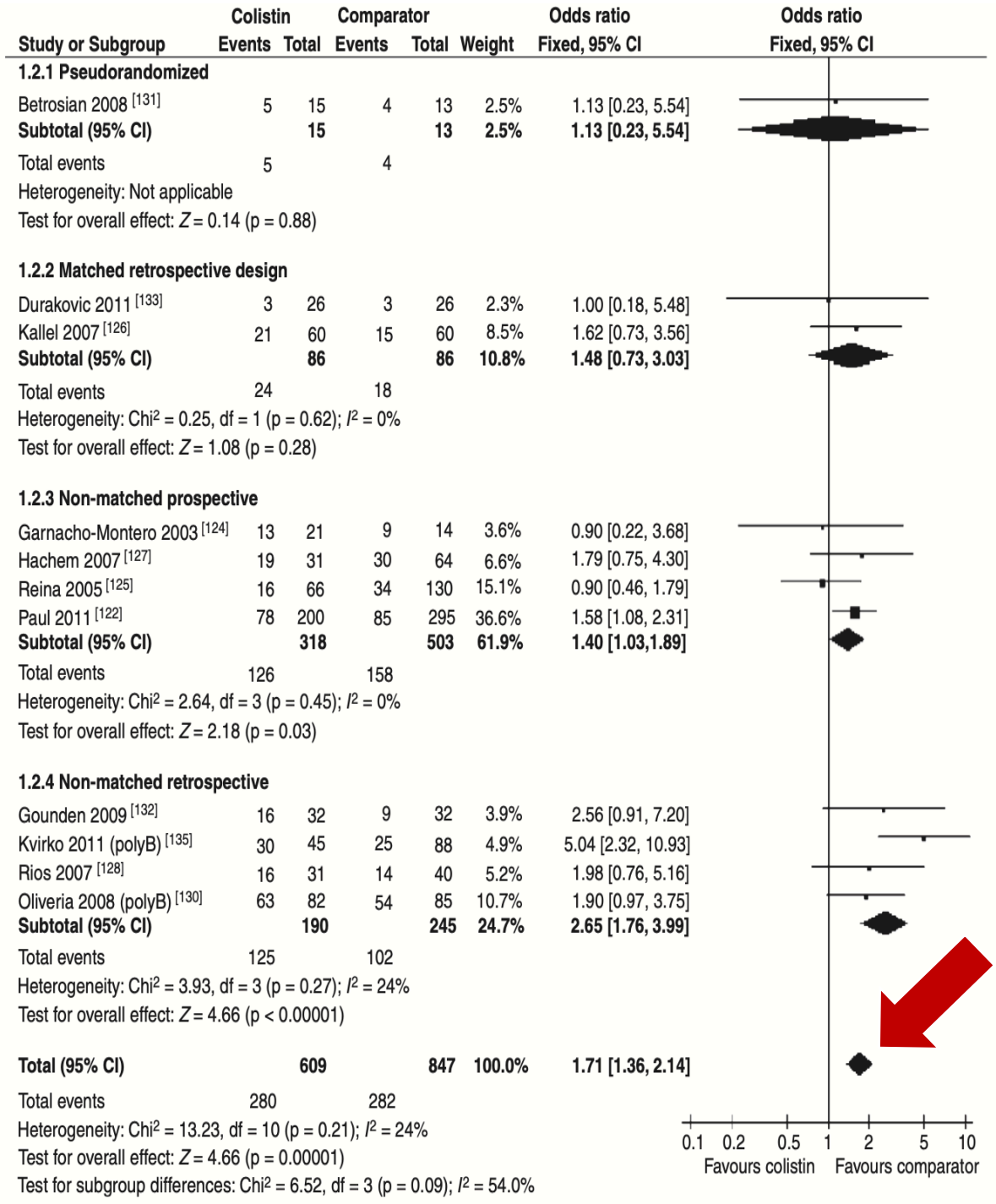
# Treatment with COLISTIN
# MDR *P. aeruginosa* infections

| Nosocomial infections Total n = 121 | Favorable clinical response, n (%) | Crude mortality, n (%) | Microbiological outcome, n (%) | |
|---|---|---|---|---|
| | | | Eradication | Non-eradication |
| Bacteremia (n = 16) | 10 (62.5) | 6 (37.5) | 7 (43.8) | 6 (37.5) |
| Pneumonia (n = 20) | 13 (65) | 7 (35) | 6 (30) | 7 (35) |
| Bronchial infection (n = 59) | 43 (72.9) | 6 (10.2) | 9 (15.3) | 36 (61) |
| Urinary (n = 13) | 11 (84.6) | 1 (7.7) | 3 (23.1) | 6 (46.2) |
| Skin and soft tissues (n = 11) | 8 (72.7) | 0 | 5 (45.5) | 3 (27.3) |
| Otitis (n = 1) | 1 (100) | 0 | 1 (100) | 0 |
| Arthritis (n = 1) | 1 (100) | 0 | 0 | 0 |

Montero M, et al Infection 2009 Oct;37(5):461-5.




# Treatment with COLISTIN for MDR *P. aeruginosa* infections

Yahav et al. Clin Microbiol Infect 2012: 18: 18-29

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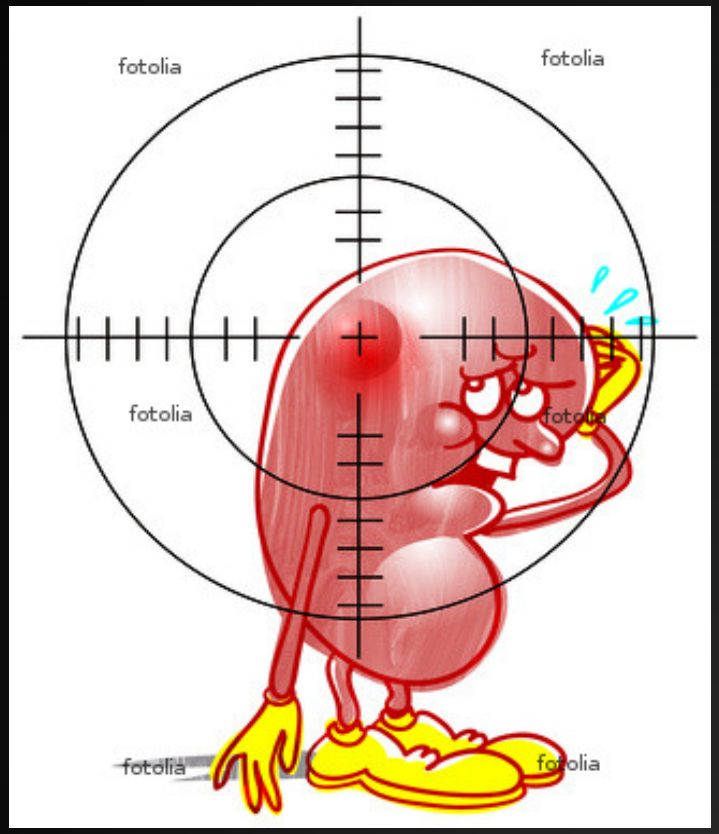
# Impact of colistin plasma levels on the clinical outcome of patients with infections caused by extremely drug-resistant *Pseudomonas aeruginosa*




**Nephrotoxicity**

**From 40% to 70% of patients**

Dosage required to treat systemic infections approach the **threshold for nephrotoxicity** making the **therapeutic window very narrow**

Kengkla K, J Antimicrob Chemother. 2018;73:22-32
Sorli L, et al. BMC Infect Dis 2013; 13:380

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# Role of aminoglycoside

- Multicenter restrospective cohort study of prospectively collected data from 2010-2017, 6 university hospitals in Spain (4), Argentina (1) and Turkey (1).
- 542 GNB-BSI: 304 (56%) combination; 52% of them **cefepime plus amikacin**
- 146 episodes-MDR: ESBL + 45.2%; CRE 8.2%
- Median days of **aminoglycosides 2 (IQR 1-3)**

**TABLE 4** Case fatality and nephrotoxicity rates at different assessment points

| Treatment | No. (%) in study population | | | |
|---|---|---|---|---|
| | Total ($n = 542$) | Combination therapy ($n = 304$) | Monotherapy ($n = 238$) | $P^a$ |
| 7-day case fatality rate | 49 (9) | 18 (5.92) | 31 (13) | 0.007 |
| 30-day case fatality rate | 115 (21.2) | 48 (15.8) | 67 (28.1) | 0.001 |
| Persistent BSI[b] | 24 (4.4) | 7 (2.4) | 17 (7.20) | 0.014 |
| Incidence of nephrotoxicity at end of antibiotic treatment | 40 (7.4) | 18 (5.9) | 22 (9.2) | 0.2 |

[a]Qualitative data were tested by the chi-square test.

[b]BSI: bloodstream infection. Percentages are calculated based on the available data regarding persistent BSI (total study population, $n = 533$; monotherapy population, $n = 236$; combination therapy population, $n = 297$).

Albasanz-Puig et al. AAC 2021

# Is combination with AG a solution?

**TABLE 1** Clinical and demographic characteristics of patients with BSI episodes presenting with and without septic shock[c]

| Characteristic | All episodes ($n$ = 1,563) | No septic shock ($n$ = 1,306) | Septic shock ($n$ = 257) | $P$ value |
|---|---|---|---|---|
| Demographic data | | | | |
| Age, median (IQR), yr | 59 (48–67) | 61 (51–69) | 59 (47–66) | 0.616 |
| Male sex | 918 (59) | 768 (59) | 150 (58) | 0.896 |
| Underlying disease | | | | |
| Hematological malignancy | 1,348 (86) | 1,168 (89) | 180 (70) | <0.001 |
| Solid neoplasm[a] | 238 (15) | 157 (12) | 81 (32) | <0.001 |
| Hematopoietic stem cell transplant | 400 (26) | 355 (27) | 45 (18) | 0.001 |
| Allogenic/autologous | 249/151 (62/38)[b] | 215/140 (61/39)[b] | 34/11 (76/24)[b] | 0.051 |
| Any comorbidity | 456 (29) | 366 (28) | 90 (35) | 0.024 |
| Corticosteroid therapy | 588 (38) | 461 (35) | 127 (49) | <0.001 |
| Nosocomial BSI (vs health care or community acquired) | 999 (64) | 883 (68) | 116 (45) | <0.001 |
| Source of BSI | | | | |
| Endogenous/unknown | 763 (49) | 650 (50) | 113 (44) | 0.089 |
| Catheter related | 333 (21) | 309 (24) | 24 (9) | <0.001 |
| Abdominal | 102 (7) | 72 (6) | 30 (12) | <0.001 |
| Pulmonary | 97 (6) | 49 (4) | 48 (19) | <0.001 |
| Urinary | 83 (5) | 62 (5) | 21 (8) | 0.025 |
| Inappropriate empirical antibiotic therapy | 471 (30) | 426 (32.6) | 45 (17.5) | <0.001 |
| For Gram-positive cocci | 290 (18.6) | 277 (21.2) | 13 (5.1) | <0.001 |
| For Gram-negative bacilli | 146 (9.3) | 121 (9.3) | 25 (9.7) | 0.816 |
| Outcome | | | | |
| Mechanical ventilation requirement | 100 (6.6) | 29 (2.3) | 71 (27.6) | <0.001 |
| 30-day mortality | 342 (21.9) | 201 (15.4) | 141 (54.9) | <0.001 |

[a]There were 25 patients who had both a hematological malignancy and a solid neoplasm.
[b]Percentage among hematopoietic stem cell transplant recipients.
[c]Abbreviations: IQR, interquartile range; BSI, bloodstream infection. All values except age are shown as no. (%).



Chumbita et al. AAC 2021



# Is combination with AG a solution?

## The combination works well when both drugs are active *in vitro*

**TABLE 3** Mortality according to active empirical antibiotic coverage administered in Gram-negative bloodstream infection with septic shock[a]

| Active antibiotic(s) | Survival, *n* (%) | Death, *n* (%) |
|---|---|---|
| Only 1 $\beta$-lactam was active ($n = 64$) | 22 (34) | 42 (66) |
| Only amikacin was active ($n = 10$) | 1 (10) | 9 (90) |
| Combined $\beta$-lactam and amikacin were both active ($n = 101$) | 62 (61) | 39 (39) |
| Combined $\beta$-lactam, quinolone, and amikacin were all active ($n = 4$) | 2 (50) | 2 (50) |
| Combined $\beta$-lactam and quinolone were both active ($n = 6$) | 4 (67) | 2 (33) |
| No active empirical antibiotic was administered ($n = 22$) | 3 (14) | 19 (86) |

[a]*P* value for all data is $<0.001$.

Chumbita et al. AAC 2021

We probably **cannot count on aminoglycoside** getting us through the first one or two days of the infection if **this is the only antibiotic that is active...**

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# Old versus new antibiotics against MDR *Pseudomonas aeruginosa*

## OLD

- Colistin
- Aminoglycoside

## NEW

- Ceftolozano-tazobactam
- Ceftazidime avibactam
- Imipenem-relebactam
- Cefiderocol

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# 4- Ceftolozano-tazobactam

# Ceftolozane-tazobactam

- High affinity for PBPs:
  - *P. aeruginosa*: PBP1b, PBP1c, PBP3.
  - *E. coli*: PBP3
- Higher **stability** against AmpC-type β-lactamases
- Increased permeability of the g(-) outer membrane:
  - Overcomes the effect of efflux pumps and porin mutations.
- Greater activity against *P. aeruginosa* than other anti-PA drugs
- Tazobactam inhibits several β-lactamases including ESBL

Sucher AJ, et al. Ann Pharmacother. 2015:49(9):1046-56
Cho JC, Pharmacotherapy. 2015; 35(7):701-15.

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# RCT: Ceftolozane-tazobactam versus meropenem for treatment of nosocomial pneumonia (ASPECT-NP)

| | Ceftolozane–tazobactam group | Meropenem group | % difference (95% CI)* |
|---|---|---|---|
| Gram-negative pathogens | 157/259 (60·6%) | 137/240 (57·1%) | 3·5 (–5·1 to 12·1) |
| Enterobacteriaceae | 120/195 (61·5%) | 105/185 (56·8%) | 4·8 (–5·1 to 14·5) |
| ESBL-producing Enterobacteriaceae | 48/84 (57·1%) | 45/73 (61·6%) | –4·5 (–19·3 to 10·7) |
| *Pseudomonas aeruginosa* | 36/63 (57·1%) | 39/65 (60·0%) | –2·9 (–19·4 to 13·8) |
| Multidrug-resistant *P aeruginosa* | 13/24 (54·2%) | 6/11 (54·5%) | –0·4 (–31·2 to 31·7) |
| Extensively drug-resistant *P aeruginosa* | 4/10 (40·0%) | 2/5 (40·0%) | 0·0 (–43·6 to 40·3) |

Data are n/N (%). *Unstratified Newcombe CIs; inferences drawn from these intervals might therefore not be reproducible.

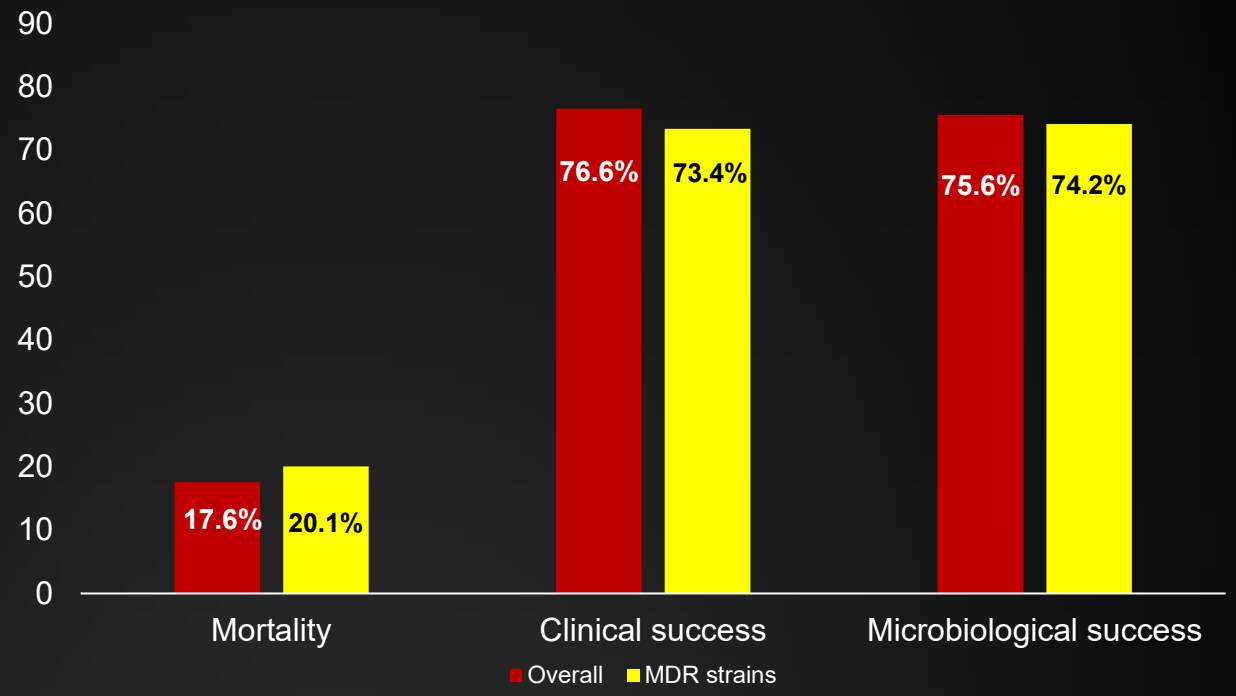
***Table 3:*** **Per-pathogen clinical cure at test-of-cure visit in the microbiological intention-to-treat population**

Kollef et al. Lancet Infect Dis 2019; 19(12): 1299-311

# Clinical experience with ceftolozane-tazobactam in *P. aeruginosa* infections

**12 studies**

including 2 comparative studies versus polymyxin or aminoglycoside




Yahav et al CMR 2020

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# Retrospective comparative study of ceftolozane-tazobactam vs. colistin/aminoglycoside in *P. aeruginosa* MDR infections

- 200 patients (100 per arm)
- 70% ICU, 63% ventilated, 42% severe sepsis or shock
- VAP 52%; concomitant BSI 7%
- Combined therapy 72% in the colistin arm vs 15% in TOL/TAZ

| Outcome | Ceftolozane/ Tazobactam (N = 100) | Polymyxin/Aminoglycoside (N = 100) | *P* Value |
|---|---|---|---|
| Clinical cure | 81 | 61 | .002 |
| In-hospital mortality | 20 | 25 | .40 |
| Acute kidney injury | 6 | 34 | <.001 |

Pogue et al . CID 2020;71:304

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# Retrospective comparative study of ceftolozane-tazobactam vs. BAT in LRTI due to MDR/XDR *P. aeruginosa*

| Outcomes | C/T ($n$ = 118) | Best alternative ($n$ = 88) | $P$ value |
|---|---|---|---|
| Primary outcome | | | |
| Composite clinical failure | 28 (23.7) | 43 (48.9) | < 0.001 |
| 30-day mortality | 18 (15.3) | 18 (20.5) | 0.331 |
| Adverse drug reaction, any | 12 (10.2) | 29 (33.0) | < 0.001 |

**Table 4** Multivariable logistic regression for factors independently associated with clinical failure

| Variables | OR | $P$ value | 95% CI | aOR | $P$ value |
|---|---|---|---|---|---|
| C/T treatment group | 0.326 | < 0.001 | 0.179–0.591 | 0.267 | < 0.001 |
| APACHE II score | 1.088 | < 0.001 | 1.042–1.137 | 1.102 | < 0.001 |

C/T was associated with a 73.3% reduction in clinical failure despite having longer time to active therapy (2.3 vs. 0.7 days)

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Holger et al. Infect Dis Ther 2022; 11(5):1965-1980

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# Delays in Time to Effective Therapy

- Multicenter, retrospective study describing the use of C/T for MDR *P. aeruginosa* in 20 hospitals across the US
  - C/T susceptibility was not required for enrollment
  - Median time to C/T initiation: 9 days after culture collection
- C/T initiation within 4 days after culture collection was associated with:
  - **Survival:** adjusted OR: 5.55 (95% CI: 2.14-14.40)
  - **Clinical success:** adjusted OR: 2.93 (95% CI: 1.40-6.10)
  - **Microbiological cure:** adjusted OR: 2.59 (95% CI: 1.24-5.38)

Study results emphasize the **importance of early initiation of effective therapy** and **availability of susceptibility testing with timely results**

Gallagher. Open Forum Infect Dis. 2018;5;ofy280.

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# 5- Ceftazidime avibactam

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# Activity of Ceftazidime-avibactam against MDR/DR *P. aeruginosa*

51 Spanish hospitals.
1445 strains

| | | | EUCAST 2018 | |
|---|---|---|---|---|
| Antibiotic[a] | $MIC_{50}$ (mg/L) | $MIC_{90}$ (mg/L) | %S | %R |
| TIC | 32 | 256 | 18.8 | 81.2 |
| TZP | 8 | 128 | 73.5 | 26.5 |
| CAZ | 4 | 32 | 79.7 | 20.3 |
| FEP | 4 | 16 | 79.4 | 20.6 |
| COZ/TZB | 1 | 2 | 94.6 | 5.4 |
| CAZ/AVI | 2 | 8 | 94.2 | 5.8 |
| ATM | 4 | 32 | – | 14.8 |
| IPM | 2 | 16 | 72.8 | 15.6 |
| MEM | 1 | 16 | 70.1 | 14.1 |
| CIP | 0.25 | >16 | 61.6 | 38.4 |
| TOB | 0.5 | 32 | 83.7 | 16.3 |
| AMK | 4 | 8 | 91.6 | 4 |
| CST | 1 | 2 | 94.6 | 5.4 |

Del Barrio-Tofiño et al. J Antimicrob Chemother. 2019:74:1825-1835

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

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

# RCT: Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including VAP (REPROVE)

| | Patients with clinical cure (clinically evaluable population) | | | Patients with favourable microbiological response* (extended microbiologically evaluable population) | | |
|---|---|---|---|---|---|---|
| | Ceftazidime-avibactam (n=257) | Meropenem (n=270) | % difference (95% CI) | Ceftazidime-avibactam (n=125) | Meropenem (n=131) | % difference (95% CI) |
| **Enterobacteriaceae** | | | | | | |
| *Klebsiella pneumoniae* | 31/37 (83·8%) | 39/49 (79·6%) | 4·2 (–13·49 to 20·50) | 29/37 (78·4%) | 39/49 (79·6%) | –1·2 (–19·60 to 15·96) |
| *Enterobacter cloacae* | 20/21 (95·2%) | 7/11 (63·6%) | 31·6 (4·79 to 61·30) | 18/21 (85·7%) | 7/11 (63·6%) | 22·1 (–8·07 to 53·69) |
| *Escherichia coli* | 8/11 (72·7%) | 14/18 (77·8%) | –5·1 (–39·26 to 25·79) | 10/11 (90·9%) | 16/18 (88·9%) | 2·0 (–29·11 to 26·44) |
| *Proteus mirabilis* | 11/11 (100·0%) | 7/8 (87·5%) | 12·5 (–16·54 to 48·07) | 9/11 (81·8%) | 6/8 (75·0%) | 6·8 (–30·73 to 46·51) |
| *Serratia marcescens* | 10/12 (83·3%) | 8/8 (100·0%) | –16·7 (–45·58 to 19·48) | 9/12 (75·0%) | 5/8 (62·5%) | 12·5 (–27·47 to 51·82) |
| *Enterobacter aerogenes* | 4/6 (66·7%) | 2/5 (40·0%) | 26·7 (–31·92 to 70·73) | 5/6 (83·3%) | 3/5 (60·0%) | 23·3 (–31·30 to 68·33) |
| **Gram-negative pathogens other than Enterobacteriaceae** | | | | | | |
| *Pseudomonas aeruginosa* | 27/42 (64·3%) | 27/35 (77·1%) | –12·8 (–32·25 to 8·01) | 18/42 (42·9%) | 14/35 (40·0%) | 2·9 (–19·13 to 24·32) |
| *Haemophilus influenzae* | 10/11 (90·9%) | 11/13 (84·6%) | 6·3 (–26·19 to 36·09) | 11/11 (100·0%) | 12/13 (92·3%) | 7·7 (–20·08 to 34·00) |
| **Gram-positive aerobes** | | | | | | |
| *Staphylococcus aureus* | 11/14 (78·6%) | 16/22 (72·7%) | 5·8 (–25·24 to 32·67) | 5/14 (35·7%) | 17/22 (77·3%) | –41·6 (–67·04 to –8·36) |

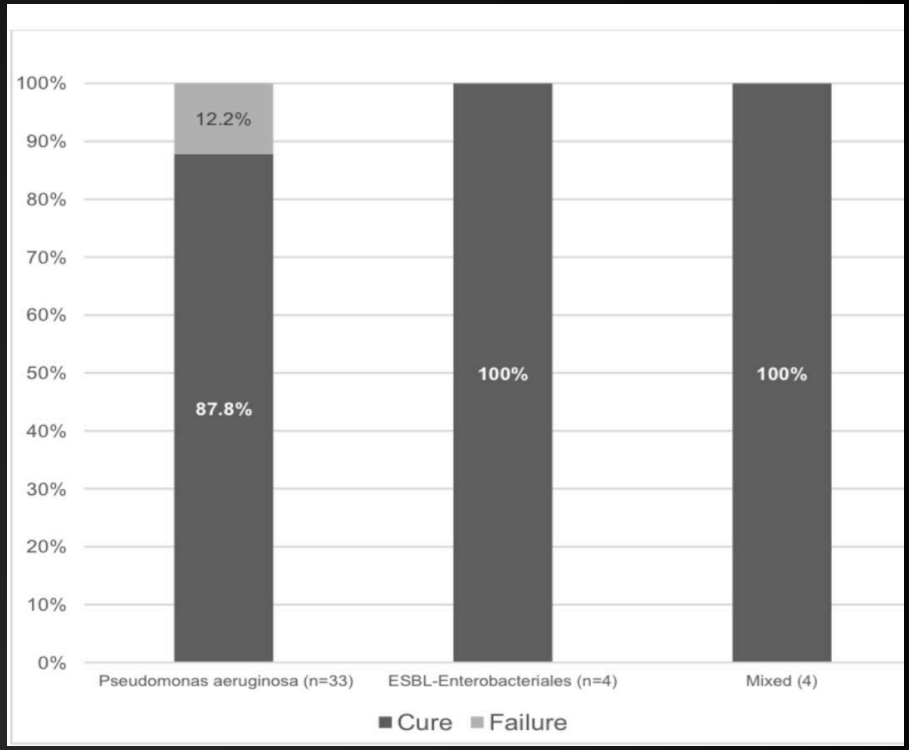
*Eradication or presumed eradication of the baseline pathogens.

***Table 2:*** **Per-pathogen clinical cure rates and favourable microbiological response rates at test-of-cure visit**

Torres et al. Lancet Infect Dis 2018;18: 285-95

# Ceftazidime-avibactam for the treatment of infections due to MDR Gram-negative bacteria other than CRE

- **Clinical cure** was achieved in **90.2%** (37/41) of patients
- The only factor related to **clinical failure** was receipt of **continuous RRT** at infection onset
- Development of resistance to **CAZ-AVI was not detected** in any patients during the follow-up period
- No treatment-related AEs were observed




Vena A, et al. Antibiotics (Basel) 2020;9:71

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

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

# Ceftolozane-Tazobactam Versus Ceftazidime-Avibactam for the Treatment of Infections Caused by Multidrug-Resistant *Pseudomonas aeruginosa:* a Multicenter Cohort Study

Almangour M et al. Antim Agents Chemoth 2023

- 200 pts with *P.aeruginosa* infections 100 w C/A VS 100 w C/T
- Overall, 37/200 (19%) had BSI.
- Most common site of infection: HAP/VAP (49%), wound (23.5%) and UTI (10.5%)
- COMBO therapy: 47% pts in C/T VS 35% in C/A (p= 0.084).

| Outcome[a] | C-T (*n* = 100) | CAZ-AVI (*n* = 100) | *P* Value | Odds Ratio (95% CI) | Adjusted Odds[b] Ratio (95% CI) |
|---|---|---|---|---|---|
| Clinical cure | 61 | 66 | 0.463 | 0.81 (0.43 to 1.49) | 0.92 (0.41 to 2.05) |
| In-hospital mortality | 44 | 37 | 0.314 | 1.34 (0.76 to 2.36) | 1.13 (0.52 to 2.48) |
| 30-day mortality | 27 | 23 | 0.514 | 1.24 (0.65 to 2.35) | 1.20 (0.48 to 3.00) |
| Infection-related mortality | 25 | 19 | 0.307 | 1.42 (0.72 to 2.79) | 1.00 (0.40 to 2.52) |
| Microbiologic outcome[c] | | | | | |
| Eradication | 46 | 43 | 0.843 | 0.94 (0.46 to 1.89) | |
| Persistence | 32 | 28 | | | |
| 30-day readmission[d] | 11 | 14 | 0.73 | | |
| 30-day readmission due to infection[d] | 5 | 8 | 0.511 | | |
| 30-day recurrence[d] | 8 | 13 | 0.364 | | |
| 90-day recurrence[d] | 14 | 16 | 0.96 | | |
| Length of hospital stay from onset of infection (days) | 30 (20 to 75) | 32 (17 to 66) | 0.61 | | |
| Length of ICU stay from onset of infection (days)[e] | 25 (9 to 44) | 24 (14 to 40) | 0.829 | | |
| Duration of mechanical ventilation (days)[f] | 23 (7 to 45) | 21 (8 to 42) | 0.874 | | |
| Acute kidney injury | 23 | 17 | 0.289 | 1.46 (0.69 to 3.14) | 1.74 (0.66 to 4.59) |

**NS**

# 6- Imipenem-relebactam

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

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

# Imipenem-relebactam and MDR *P. aeruginosa*

- Relebactam potentiates the activity of impenem against CR-PA by hyperproduction of AmpC and loss of OprD porin.
- It has no effect against metallo- β lactamases.
- Imipenem and relebactam are not substrate of efflux pumps.

**US study** **(Lob AAC 2017)**

- $MIC_{90/50}$ = 4/2 µg/mL (8 times lower than IMI alone (32/16 µg/mL).
- Only 6.8% were resistant

Lob SH, Antimicrob. Agents Chemother. 2017;61:1-9.
Livermore DM, J. Antimicrob. Chemother. 2013;68:2286-2290

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

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

# Cross-resistance of Ceftolozane/Tazobactam and Imipenem/Relebactam Against Clinical *P. aeruginosa* Isolates from Bloodstream and Respiratory Tract Infections – SMART United States 2019-2021

- To evaluate the activity of C/T and IMI/REL against 1938 *P. aeruginosa* isolates collected from pts with LRTI and BSI in the US (SMART program)

- Among *P.aeruginosa*, 96% and 90% were susceptible to C/T and IMI/REL, respectively. All tested first-line β-lactams, including CARBA, showed activity < 81%.

Table 1. Antimicrobial susceptibility of all *P. aeruginosa* and resistant subsets

| | | % Susceptible | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Phenotype | n | C/T | IMI/REL | CZA | MEM | IMI | P/T | FEP | CAZ | ATM | LVX |
| All | 1986 | 96.2 | 90.4 | 94.5 | 78.0 | 64.2 | 76.9 | 80.9 | 79.1 | 69.4 | 65.6 |
| MDR | 287 | 77.7 | 56.8 | 66.6 | 22.3 | 15.7 | 8.7 | 12.2 | 12.9 | 3.8 | 21.3 |
| DTR | 143 | 72.7 | 37.1 | 51.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| MEM-NS | 436 | 88.5 | 57.8 | 79.4 | 0.0 | 5.0 | 39.4 | 47.7 | 48.6 | 25.9 | 27.6 |
| C/T-NS | 75 | 0.0 | 57.3 | 44.0 | 33.3 | 26.7 | 18.7 | 6.7 | 1.3 | 8.0 | 22.7 |
| IMI/REL-NS | 190 | 83.2 | 0.0 | 69.5 | 3.2 | 0.5 | 31.1 | 34.7 | 42.1 | 16.8 | 15.3 |
| CZA-R | 109 | 61.5 | 46.8 | 0.0 | 17.4 | 20.2 | 10.1 | 4.6 | 0.0 | 5.5 | 19.3 |

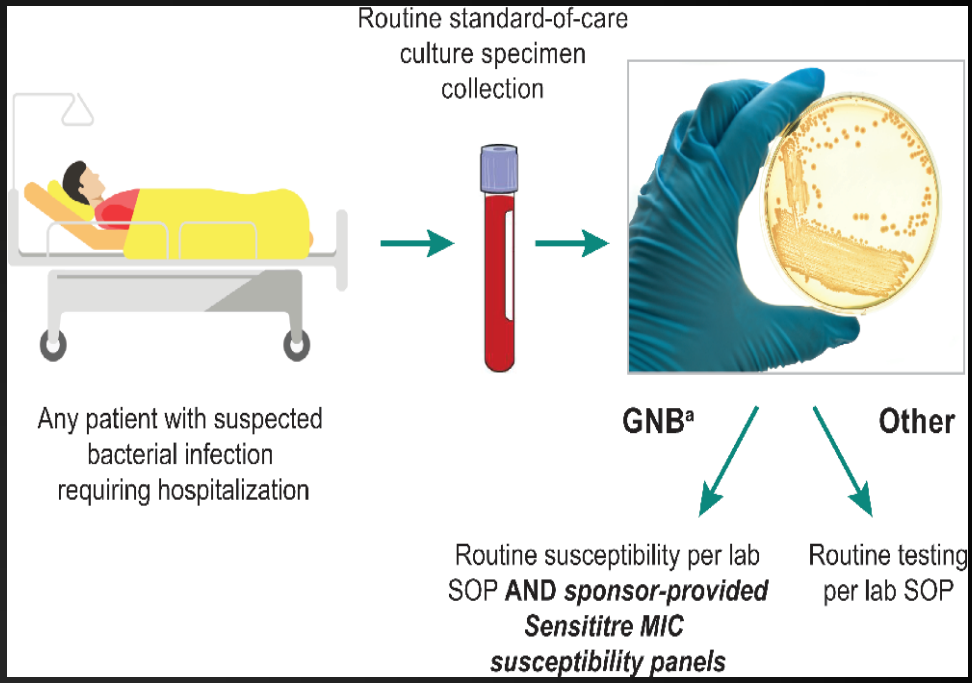
Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Lob S, Poster 2154 ID week Boston 2023

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

# Imipenem-relebactam

- Tested against **CR-GNB** in an RCT, in the RESTORE-IMI 1 trial.
- HAP, VAP, UTI and IAI caused by CR-GNB, of which CRPA was the most common (16/21 pts IMI-REL and 8/10 allocated to COLI + IMI)
- A favourable overall response to treatment at 28 davs was observed in 13/16 **(81%) with IMI-REL** compared with 5/8 **(63%) with COLI+IMI**, adjusted difference 3.1 (95% CI 19.8 to 38.2)



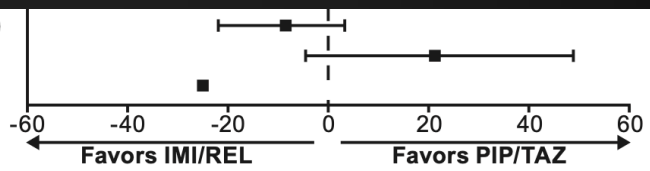

Motsch J, Clin Infect Dis. 2020;70(9):1799-1808.

# Imipenem-relebactam in HABP/VAP. RESTORE IMI-2

## Baseline *P.aeruginosa* 34 (15.8) IMI/REL vs 48 (22.0) P/Tz

| Favorable clinical rensponse | IMI/REL n/N (%) | PIP/TAZ n/N (%) | Adjusted difference (95% CI) |
|---|---|---|---|
| Enterobacterales[d] | 45/68 (66.2%) | 43/66 (65.2%) | 4.7 (-10.9, 20.0) |
| *Pseudomonas. aeruginosa*[e] | 7/15 (46.7%) | 17/25 (68.0%) | -21.3 (-49.7, 10.0) |
| *Acinetobacter calcoaceticus-baumannii* | 1/1 (100.0%) | 4/4 (100.0%) | 0.0[f] |

| 28-day mortality | | | |
|---|---|---|---|
| Enterobacterales[d] | 8/68 (11.8%) | 13/66 (19.7%) | -8.5 (-21.9, 3.3) |
| *Pseudomonas aeruginosa*[e] | 5/15 (33.3%) | 3/25 (12.0%) | 21.3 (-4.5, 48.9) |
| *Acinetobacter calcoaceticus-baumannii* complex[e] | 0/1 (0.0%) | 1/4 (25.0%) | -25.0[f] |




| Per-pathogen favorable microbiological response | IMI/REL n/N (%) | PIP/TAZ n/N (%) | Adjusted difference[a] (95% CI) |
|---|---|---|---|
| Enterobacterales[b] | 56/68 (82.4%) | 49/66 (74.2%) | 10.9% (-2.7, 25.1) |
| *Pseudomonas aeruginosa*[c] | 10/15 (66.7%) | 18/25 (72.0%) | -5.3% (-35.3, 22.7) |
| *Acinetobacter calcoaceticus-baumannii* complex[c] | 1/1 (100.0%) | 3/4 (75.0%) | 25.0% |

Titov et al. CID 2021; 73(11):4539-48

# Imipenem-relebactam in real life

- Retrospective study in 8 hospitals USA, Jan 2020 - Aug 2021.
- Respiratory infections 11/21 (52%), UTI 3/21 (14%), prosthetic infections 3/21 (14%).
- Overall, positive blood cultures 29%
- ***P. aeruginosa* (16/21, 76%)**, *K. pneumonia* (3/21, 14%), and *Proteus mirabilis* (3/21, 14%),
- **15/16 (94%) *P. aeruginosa* MDR.**
- In combination 29% (6/21) (tobramycin more frequent)
- Mortality 7/21 (33%); Clinical cure 13/21 (62%)
- Microbiological recurrence 5/21 (24%). Development of resistance in 1 case (PA)
- Adverse effects: 1 G-I, 1 encephalopathy

Rebold et al. Open Forum Infect Dis. 2021 Dec; 8(12): ofab554

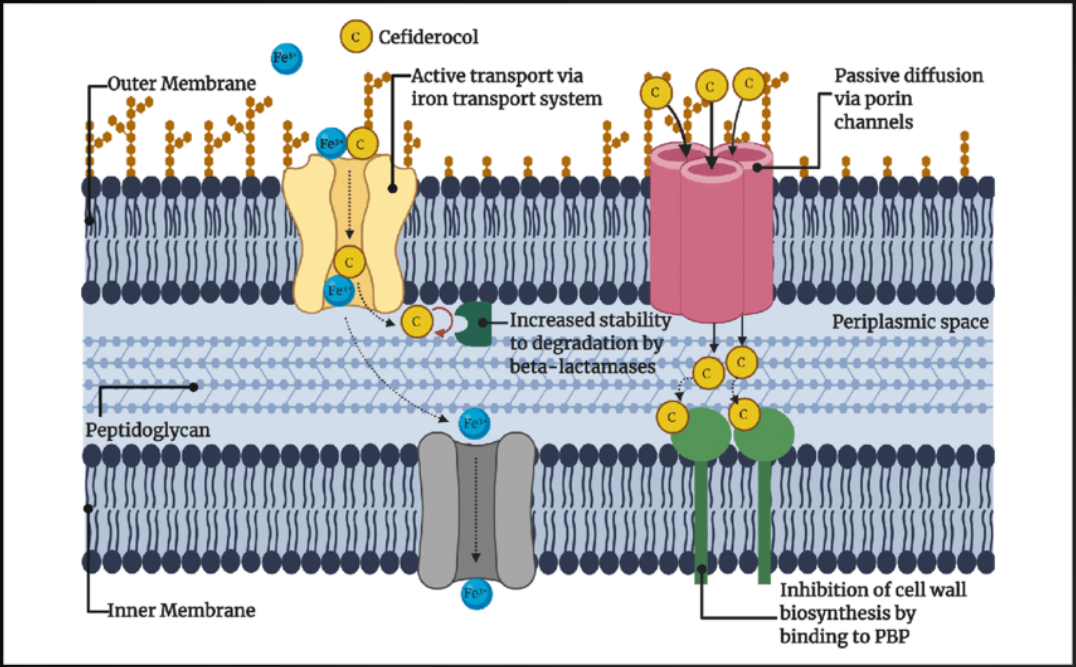
Università degli Studi di Genova
Dipartimento di Scienze della Salute (DISSAL)
Genoa, Italy

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

# 7- Cefiderocol

# Cefiderocol

Siderophore cephalosporin that uses the iron transport system to increase its periplasmic penetration.




Stable against many class A, B, C, and D beta-lactamases

Hackel MA, Antimicrob. Agents Chemother. 2017:61:1-22.
Monogue ML,. Antimicrob. Agents Chemother. 2017:61:1-10

# Activity of new antimicrobials against MDR GN

| Agent | KPC-producer | NDM-producer | OXA-48-like-producer | Carbapenem-resistant *Pseudomonas aeruginosa* | Carbapenem-resistant *Acinetobacter baumannii* | *Stenotrophomonas maltophilia* |
|---|---|---|---|---|---|---|
| Aztreonam-avibactam | | | | | | |
| Cefiderocol | | | | | | |
| Ceftazidime-avibactam[1] | | | | | | |
| Ceftolozane-tazobactam[1] | | | | | | |
| Eravacycline[1,2] | | | | | | |
| Fosfomycin (intravenous) | | | | | | |
| Imipenem-relebactam[3] | | | | | | |
| Meropenem-vaborbactam[1] | | | | | | |
| Plazomicin[1,4] | | | | | | |
| Polymyxin B[1,5] or Colistin[1,5] | | | | | | |
| Tigecycline[1,2] | | | | | | |

Tamma PD, J Pediatric Infect Dis Soc. 2019;8 (3):251-260.

# Cefiderocol CR-GNB infections. CREDIBLE study

- Randomized open-label trial
- Cefiderocol 80 vs BAT 38
- 150 patients
  - Pneumonia (n=67)
  - bacteremia (n=47)
  - UTI (n=36)

- **Microorganisms**
  - *Acinetobacter* (n=56)
  - CRE (n=60)
  - *P. aeruginosa* (n=29)

| | Cefiderocol (n=101) | Best available therapy (n=49) |
|---|---|---|
| *Acinetobacter* spp* | 21/42 (50%) | 3/17 (18%) |
| *Acinetobacter baumannii* | 19/39 (49%) | 3/17 (18%) |
| *Klebsiella pneumoniae* | 8/34 (24%) | 4/16 (25%) |
| Without *Acinetobacter* spp | 6/28 (21%) | 4/15 (27%) |
| *Pseudomonas aeruginosa* | 6/17 (35%) | 2/12 (17%) |
| Without *Acinetobacter* spp | 2/11 (18%) | 2/11 (18%) |
| *Escherichia coli* | 1/6 (17%) | 0/3 |
| Without *Acinetobacter* spp | 0/3 | 0/1 |
| *Stenotrophomonas maltophilia* | 4/5 (80%) | NA |
| Without *Acinetobacter* spp | 2/3 (67%) | NA |

Bassetti et al. Lancet Infect Dis. 2021:21(2):226-240

# Isolates with resistant phenotypes were more susceptible to cefiderocol than to comparators (EU+USA)

Cefiderocol demonstrated the highest activity against *P. aeruginosa* when compared with other antimicrobial agents

**Susceptibility of isolates with resistant phenotypes to cefiderocol and comparator agents**

| Isolates, (n) | Susceptibility, %[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | CFDC | I/R | MVB | CAZ/AVI | TZP | MEM | CST[e] | C/T |
| **Enterobacterales (8,047)** | | | | | | | | |
| CRE (169) | 87.6 | 71.0[c] | 75.7 | 81.7 | 0.6 | 10.1 | 78.7 | |
| MVB-R (41) | 70.7 | 7.3[c] | | 43.9 | 0 | 0 | 48.8 | |
| I/R-R (49) | 69.4 | | 24.5 | 40.8 | 4.1 | 10.2 | 55.1 | |
| CAZ/AVI-R (37) | 54.1 | 8.1[c] | 37.8 | | 0 | 21.6 | 56.8 | |
| BL/BLI-R (23) | 47.8 | | | | | 0 | 47.8 | |
| ***P. aeruginosa* (n=2,282)** | | | | | | | | |
| XDR (256) | 96.9 | 73.0 | | 73.4 | [d] | 7.4 | 99.2 | 72.3 |
| I/R-R (48) | 100 | | | 35.4 | [d] | 2.1 | 100 | 20.8 |
| C/T-R (60) | 85.0 | 43.3 | | 25.0 | [d] | 3.3 | 100 | |
| CAZ/AVI-R (83) | 89.2 | 47.0 | | | [d] | 8.4 | 100 | 37.3 |
| BL/BLI-R (27) | 100.0 | | | | [d] | 0 | 100 | |
| ***Acinetobacter spp.* (650)** | | | | | | | | |
| MEM-R (306) | 91.5[c] | | | | | | 76.4 | |

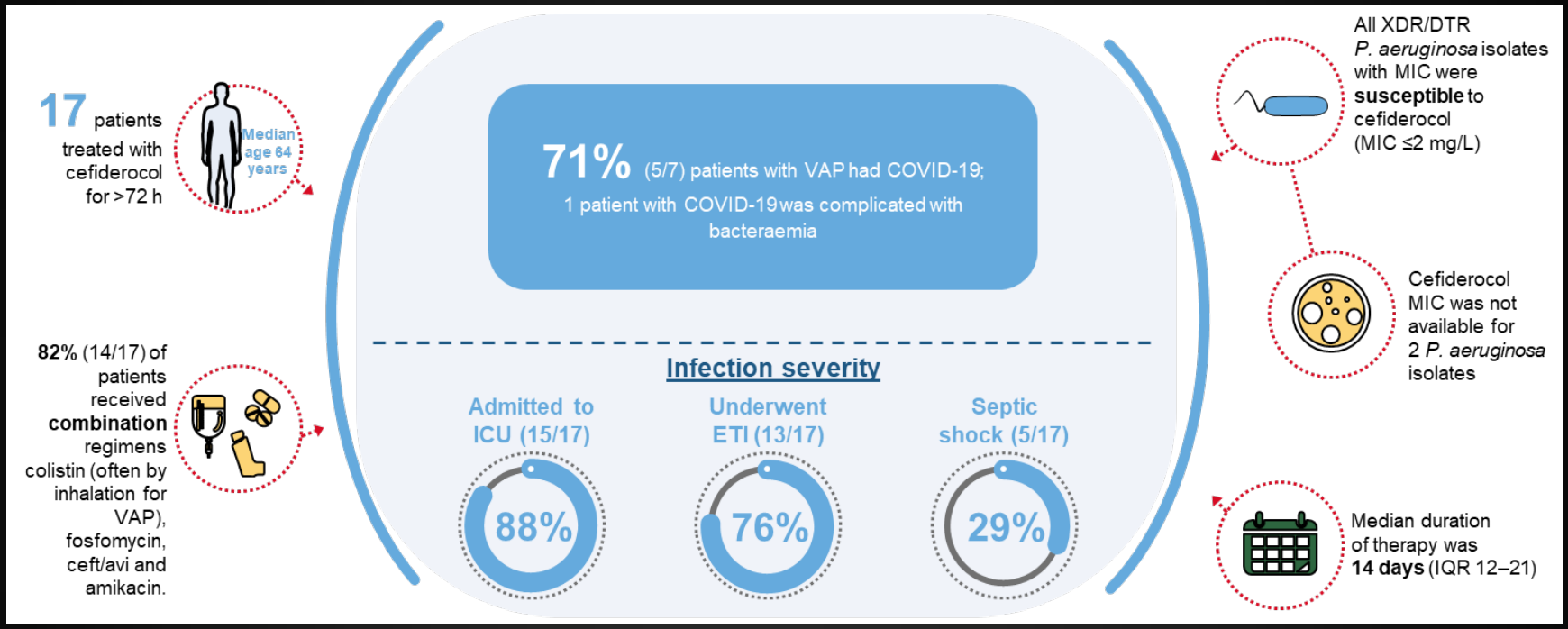
Shortridge D et al. *Microbiol Spectr* 2022;10:e0271221

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

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

# Cefiderocol in patients with XDR/DTR *P. aeruginosa* infection: a prospective, observational study

- Prospective observational study including 17 pts (median age 64 yrs) with XDR and DTR *P.aeruginosa* infections, unresponsive to BAT w/o any other available treatment options.




Meschiari M. et al. JAC Antimicrob Resist 2021;3:dlab188


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

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

# Cefiderocol in patients with XDR/DTR *P. aeruginosa* infection: a prospective, observational study

## Primary endpoints
(7 days after EOT)

**Clinical cure**

- **71%** (12/17) of patients experienced clinical cure

**Microbiological cure**

- **76%** (13/17) of patients experienced microbiological cure

**Cefiderocol was administered in all but one patient as a rescue therapy after experiencing failure of previous.**

## Secondary endpoints

**Day 30 ACM**


**4/17** patients

**Day 90 ACM**


**6/17** patients

- ACM was assessed at 30 and 90 days from start of cefiderocol therapy
- The **median time to death was 8 days** (IQR 3–10) from the EOT; only two deaths were associated with both clinical and microbiological failures

- No breakthrough infections were observed during cefiderocol therapy
- Clinical relapse was observed in 3/17 (18%) patients; median time from cefiderocol discontinuation to relapse/recurrence was 10 days (IQR 10–12)

These favourable outcomes are even **more relevant** since almost 90% pts were in ICU and 30% of the cases were critically ill.

Meschiari M. et al. JAC Antimicrob Resist 2021;3:dlab188

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

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

# 8- Conclusions

# Conclusions

- Resistance in *P.aeruginosa* is complex and driven by various mechanisms (eg, porin reduction, β-lactamase, efflux pumps).
- Because of side effects and low efficacy, colistin and aminoglycosides should no longer be used for treatment of serious *P.aeruginosa* infections.
- In light of the accumulated clinical experience and its mechanism of action, ceftolozane-tazobactam should be considered **the first choice agent** for infections caused by MDR *P.aeruginosa.*
- Ceftazidime-avibactam also represent a good treatment options, but attention should be given to the potential negative ecological impact.

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

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy

# Conclusions

- Resistance to IMI/REL and cefiderocol was not common among recent clinical isolates of *P. aeruginosa.*
- Even if further real life studies are needed, both agents represent important treatment options.
- Current data suggest that susceptibility to all new antibiotics should be tested.

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

Clinica Malattie Infettive
Ospedale Policlinico San Martino IRCCS
Genoa, Italy