Il paziente critico con infezione da germi gram negativi multiresistenti:

Pseudomonas resistente ai carbapenemi

19/6/2025

Dott.ssa Chiara Montrucchio
Ospedale Amedeo di Savoia/Oftalmico
Mal Infettive Div Ospedaliera

DEFINIZIONI

- *Pseudomonas aeruginosa* is a common cause of nosocomial infections, being responsible for about 7% of all health-care associated infections [1]
- *P. aeruginosa* multidrug-resistant (MDR)/extensively drug-resistant (XDR)
  - MDR= is defined as being not susceptible to at least one antibiotic in at least three antibiotic classes to which it is usually susceptible
  - XDR Pseudomonas is defined when there is non-susceptibility to at least one antimicrobial agent in all but two or fewer antimicrobial classes
  - 2018 “difficult-to-treat resistance” (DTR) = non-susceptibility to all of the following: ceftazidime, cefepime, piperacillin-tazobactam, imipenem-cilastatin, meropenem, ciprofloxacin, levofloxacin, and aztreonam [2]
- Ability to quickly acquire resistance to ongoing treatments
- CRPA are associated with a 30-day mortality of 32.8% and an attributable mortality of 19% [3]
- 2017: ESKAPE pathogens, a set of six microorganisms (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii,* ***Pseudomonas aeruginosa****, and Enterobacter spp*.) [4]

1 - Magiorakos A.-P., Srinivasan A., Carey R.B., Carmeli Y., Falagas M.E., Giske C.G., Harbarth S., Hindler J.F., Kahlmeter G., Olsson-Liljequist B., et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: An international expert proposal for interim standard definitions for acquired resistance. Clin. Microbiol. Infect. 2012;18:268–281. doi: 10.1111/j.1469-0691.2011.03570.x.

2- Kadri S.S., Adjemian J., Lai Y.L., Spaulding A.B., Ricotta E., Prevots D.R., Palmore T.N., Rhee C., Klompas M., Dekker J.P., et al. Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and Outcome of Resistance to All First-line Agents. Clin. Infect. Dis. 2018;67:1803–1814. doi: 10.1093/cid/ciy378.

3- Falcone M, Tiseo G, Carbonara S, et al. Mortality attributable to bloodstream infections caused by different carbapenem-resistant Gram-negative bacilli: results from a nationwide study in Italy (ALARICO Network). Clin Infect Dis 2023; 76:2059–2069.

4- World Health Organization Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics. 2017.

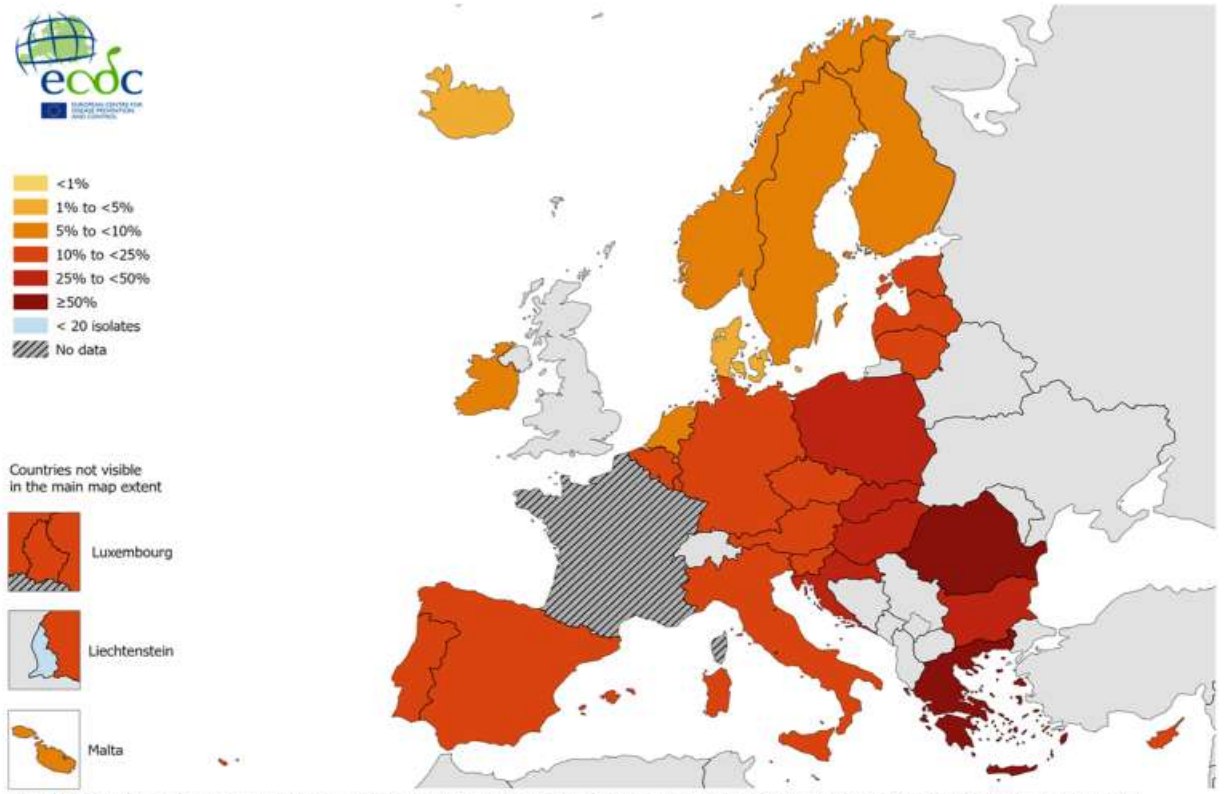
Pseudomonas aeruginosa Carbapenemi R (MDRO)

Europa
2020: 17.9%
2021: 18.1%
2022: 20.0%
2023: 18.6%

Italia
2020: 15.9%
2021: 16.4%
2022: 16.5%
2023: 17.1%

ASL CdT Invasivi
2020: 15.3%
2021: 7.4%
2022: 0%
2023: 2.7%
2024 6.9 %

Figure 6. *Pseudomonas aeruginosa.* **Percentage of invasive isolates with resistance to carbapenems (imipenem/meropenem), by country, EU/EEA, 2023**



A total of **5,172** clinical isolates of ***Pseudomonas aeruginosa*** were collected during 2020–2023 from hospitalized patients in 43 centers in 17 European countries, Israel, and Turkey (1 isolate per patient infection episode)

Carbapenem resistance was **defined as MIC ≥8 mg/L to meropenem or imipenem** (CLSI criteria)

MICs were assessed **using broth microdilution according CLSI guidelines**

MIC interpretations were performed using **EUCAST breakpoints for comparators** and **FDA/EUCAST/CLSI breakpoints for cefiderocol**

Distribution of phenotypes and genotypes observed among *P. aeruginosa*

7 Mendes et al; Poster P1349

CLSI: Clinical and Laboratory Standards Institute; **EUCAST**: European Committee on Antimicrobial Susceptibility Testing; **FDA**: US Food and Drug Administration; **IMP**: imipenemase; **MIC**: minimum inhibitory concentration; **NDM**: New-Delhi metallo-beta-lactamase; **VIM**: Verona integron-encoded metallo-beta-lactamase

SENTRY Surveillance Program: *Pseudomonas aeruginosa* (2020 – 2023) I

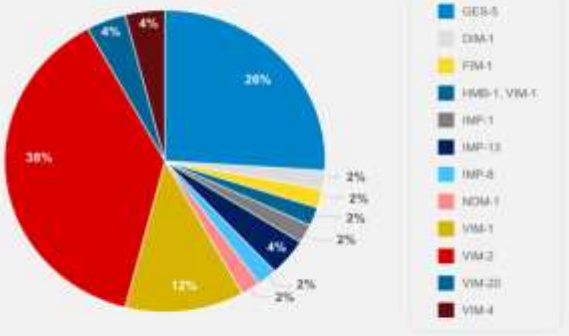
Results

Susceptibility rates of cefiderocol and comparator antibiotics against *P. aeruginosa* isolates

Country (n) Agent	France	Germany	Italy	Spain	UK
All *P. aeruginosa* (n=2,945)	632	854	790	700	289
Cefiderocol	99%	99%	98%	99%	100%
Ceftolozane-tazobactam	96%	89%	95%	96%	99%
Ceftazidime-avibactam	97%	97%	96%	97%	98%
Imipenem-relebactam	93%	98%	92%	90%	99%
Aztreonam-avibactam	82%	67%	82%	85%	49%
Carbapenem resistant (n=495)	80	147	114	126	28
Cefiderocol	96%	92%	98%	100%	100%
Ceftolozane-tazobactam	80%	93%	74%	79%	93%
Ceftazidime-avibactam	84%	91%	83%	87%	96%
Imipenem-relebactam	81%	92%	77%	79%	96%
Aztreonam-avibactam	48%	34%	24%	35%	11%
TOL-TAZ resistant (n=106)	21	14	39	27	3
Cefiderocol	81%	86%	95%	100%	33
Ceftazidime-avibactam	38%	36%	36%	63%	67
Imipenem-relebactam	48%	64%	49%	30%	33
Aztreonam-avibactam	19%	14%	13%	22%	33

n: number of isolates. Interpretations according to EUCAST breakpoint table v 14 and Guidance on what to do when no breakpoints. Cefiderocol, breakpoint of ≤2 mg/L for *Pseudomonas* and other nonfermenters. Aztreonam-avibactam is reported at percentage with MIC of mg/L.

Summary of carbapenemases for 47/495 CR *P. aeruginosa*

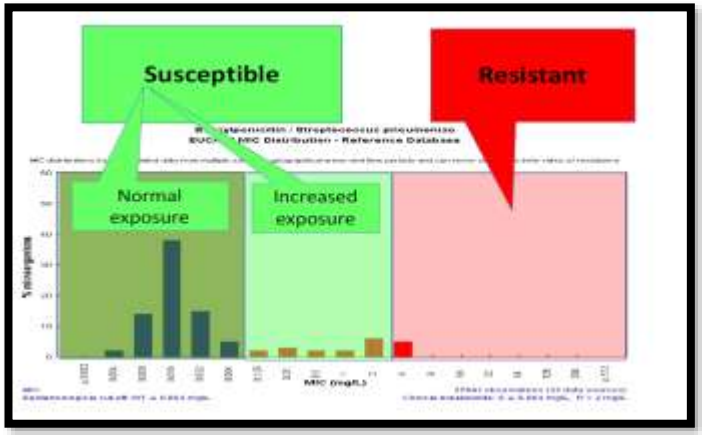


Overall isolates from all countries showed high susceptibility to comparators except aztreonam-avibactam, which was poorly active against *P. aeruginosa*

4 Longshaw et al; Poster E0723

CR: carbapenem-resistant; **DIM**: Dutch imipenemase; **FIM**: Florence imipenemase; **GES**: Guiana extended-spectrum; **HMB**: Hamburg metallo-beta-lactamase; **IMP**: imipenemase; **NDM**: New-Delhi metallo-beta-lactamase; **TOL-TAZ**: ceftolozane-tazobactam; **VIM**: Verona integron-encoded metallo-beta-lactamase

- **S - Susceptible, standard dosing regimen**: A microorganism is categorised as "Susceptible, standard dosing regimen", when there is a high likelihood of therapeutic success using a standard dosing regimen of the agent.
- **I - Susceptible, increased exposure**: A microorganism is categorised as "Susceptible, Increased exposure"" when there is a high likelihood of therapeutic success because exposure to the agent is increased by adjusting the dosing regimen or by its concentration at the site of infection.
- **R - Resistant:** A microorganism is categorised as "Resistant" when there is a high likelihood of therapeutic failure even when there is increased exposure.



List of the most common agents and breakpoints where "Susceptible, increased exposure" is the routine susceptible category. An arbitrary S breakpoint of S=0.001 ensures that isolates are never categorised as "Susceptible, standard dose" since MICs of relevant agents are always higher than the breakpoint

Table 2. Antipseudomonal agents and the dynamics of their MIC breakpoint change.

Traditional Antibiotics	EUCAST 2019 * MIC Breakpoints S≤	R>	EUCAST 2023 ** MIC Breakpoints S≤	R>	New Antibiotics	EUCAST 2019 * MIC Breakpoints S≤	R>	EUCAST 2023 ** MIC Breakpoints S≤	R>
Beta Lactams									
Cephalosporin									
Ceftazidime	8	8	0.001	8	Ceftazidime-Avibactam	8	8	8	8
Cefepime	8	8	0.001	8	Ceftolozane-Tazobactam	4	4	4	4
					Cefiderocol			2	2
Ureidopenicillin									
Piperacillin/tazobactam	16	16	0.001	16					
Carbapenem									
Imipenem-cilastatin	4	4	0.001	4	Imipenem-Cilastatin-Relebactam				
Meropenem	2	8	2	2/8	Meropenem-Vaborbactam	8	8	8	8
Doripenem			0.001	2					
Monobactam									
Aztreonam	16	16	0.001	16	Aztreonam-Avibactam				
Other antibiotics									
Polymixin									
Colistin	2	2	4	4					
Fluoroquinolones									
Ciprofloxacin	0.5	0.5	0.001	0.5					
Levofloxacin	1	1	0.001	2					
Aminoglycosides									
Gentamycin	4	4	IE	IE	Plazomicin				
Amikacin	8	16	16	16					
Tobramycin	4	4	2	2					
Fosfomycin									

Abbreviations: EUCAST, European Committee on Antimicrobial Susceptibility Testing; IE, insufficient evidence; S, susceptible; R, resistant. * EUCAST breakpoint when the new intermediate definition was introduced. ** Current EUCAST breakpoints.

Antibiotics (Basel) 2023 Feb 16;12(2):399. doi: 10.3390/antibiotics12020399. Evidence-Based Treatment of *Pseudomonas aeruginosa* Infections: A Critical Reappraisal Arta Karruli et al.

Pseudomonas wild type

Ceppo **Pseudomonas aeruginosa**

Antibiotici	MIC	S/I/R	MIC Breakpoint EUCAST S<=	R>	Note
Amikacina	<=1	S	16	16	
Ceftazidima	2	I	0.001	8	
Ceftazidime/Avibactam	2	S	8	8	
Ceftolozane/Tazobact	0.5	S	4	4	
Ciprofloxacina	0.5	I	0.001	0.5	
Colistina	1	S	2	2	Valore MIC confermato con test in microdiluizione
Imipenem	2	I	0.001	4	
Piperacillina/tazobact	16	I	0.001	16	
Tobramicina	<=1	S	2	2	
Cefepime	4	I	0.001	8	
Fosfomacina	>128	R			
Meropenem	2	S	2	8	

Enterobatteri: Test molecolare per carbapenemasi

KPC	Negativo
OXA-48	Negativo
VIM	Negativo
IMP	Negativo
NDM	Negativo

Test eseguito su ceppo di Pseudomonas aeruginosa isolato da campione di escreato

Pseudomonas wild type

	2018	2019	2020	2021
Amikacina	S	S-HE	S*	S*
Gentamicina	S	S-HE	IE	IE
Ciprofloxacina	S	S-HE	I	I
Aztreonam	S	S-HE	I	I
Ceftazidime	S	S-HE	I	I
Cefepime	S	S-HE	I	I
Ceftazidime-avibactam	S	S	S	S
Ceftolozane-tazobactam	S	S	S	S
Imipenem	S	S-HE	I	I
Meropenem	S	S	S	S

IMPATTO SU ANTIMICROBIAL STEWARDSHIP

Maggiore utilizzo di carbapenemi?

Necessità di nota esplicativa?

Il trattamento delle infezioni da *Pseudomonas* spp richiede un aumento dell'esposizione per quasi tutti gli agenti attivi, anche quando l'isolato non presenti meccanismi di resistenza acquisiti (*Pseudomonas* "wild type")

Dosages used to define breakpoints

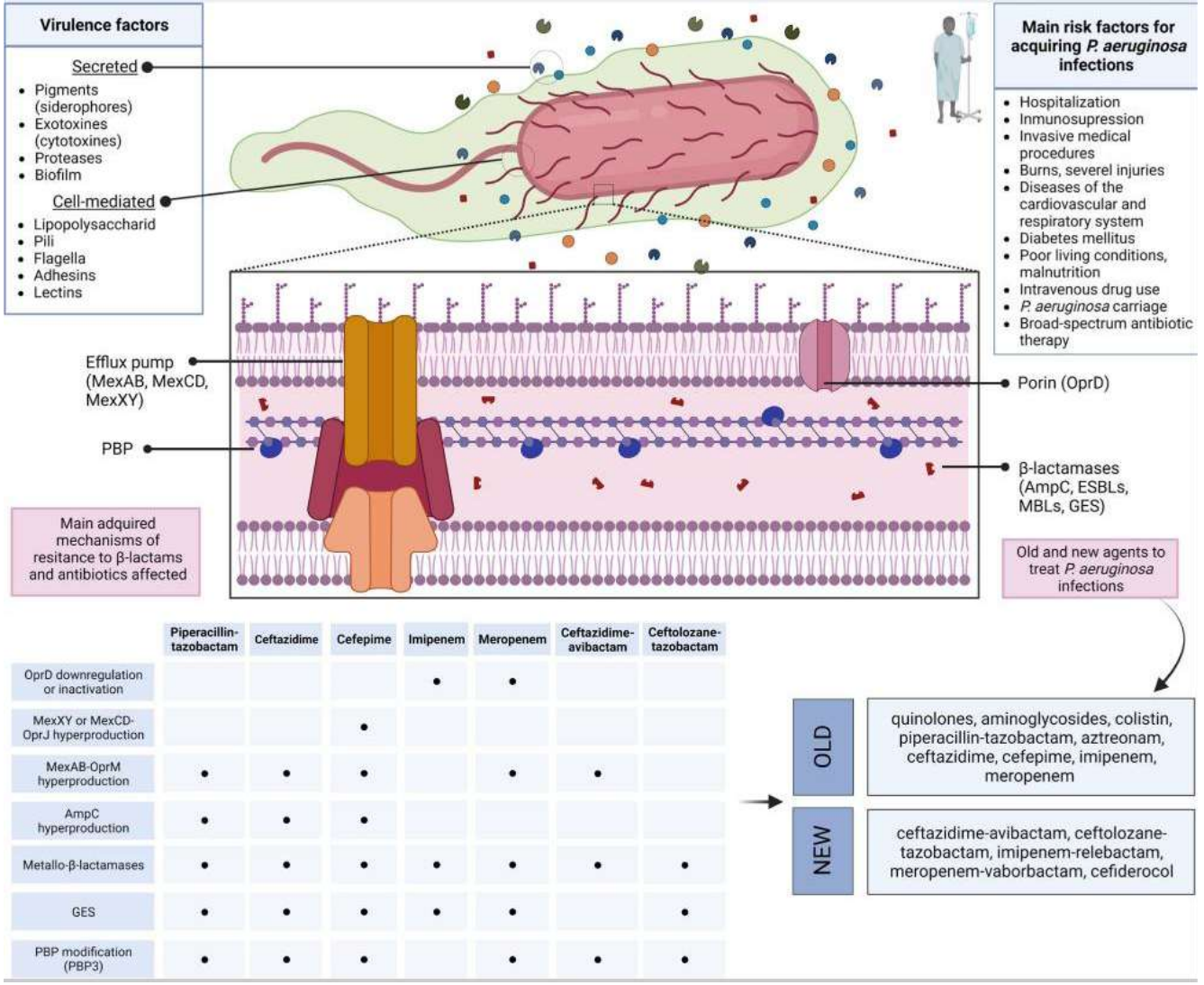
Cephalosporins	Standard dosage	High dosage	Uncomplicated UTI	Special situations
Cefaclor	0.25-0.5 g x 3 oral depending on species and/or infecti type	1 g x 3 oral		*S. aureus*: Minimum dose 0.5 g x 3 oral
Cefadroxil	0.5-1 g x 2 oral	None	0.5-1 g x 2 oral	
Cefalexin	0.25-1 g x 2-3 oral	None	0.25-1 g x 2-3 oral	
Cefazolin	1 g x 3 iv	2 g x 3 iv		*S. aureus*: High dose only
Cefepime	1 g x 3 iv or 2 g x 2 iv	2 g x 3 iv		**Severe *P. aeruginosa* infections:** 2 g x 3 with extended 4-hour infusion *S. aureus*: High dose only
Cefepime-enmetazobactam (UTI)	(2 g cefepime + 0.5 g enm	actam) x 3 iv over 2 hours		
Cefepime-enmetazobactam (hospital-acquired pneumonia, including ventilator-associated pneumonia)	(2 g cefepime + 0.5 g enm	actam) x 3 iv over 4 hours		
Cefiderocol	2 g x 3 iv over 3 hours	None		
Cefixime	0.2-0.4 g x 2 oral	None	0.2-0.4 g x 2 oral	**Uncomplicated gonorrhoea:** 0.4 g oral as a single dose
Cefotaxime	1 g x 3 iv	2 g x 3 iv		**Meningitis:** 2 g x 4 iv *S. aureus:* High dose only
Cefpodoxime	0.1-0.2 g x 2 oral	None	0.1-0.2 g x 2 oral	
Ceftaroline	0.6 g x 2 iv over 1 hour	0.6 g x 3 iv over 2 hours		***S. aureus* in complicated skin and skin structure infections:** There is some PK-PD evidence to suggest that isolates with MICs of 4 mg/L could be treated with high dose.
Ceftazidime	1 g x 3 iv	2 g x 3 iv or 1 g x 6 iv		
Ceftazidime-avibactam	(2 g ceftazidime + 0.5 g	tam) x 3 iv over 2 hours		
Ceftibuten	0.4 g x 1 oral	None		
Ceftobiprole	0.5 g x 3 iv over 2 hours	None		
Ceftolozane-tazobactam (intra-abdominal infections and UTI)	(1 g ceftolozane + 0.5 g tazobactam 3 iv over 1 hour	None		
Ceftolozane-tazobactam (hospital-acquired pneumonia, including ventilator-associated pneumonia)	(2 g ceftolozane + 1 g tazobactam x 3 iv over 1 hour	None		
Ceftriaxone	2 g x 1 iv	2 g x 2 iv or 4 g x 1 iv		**Meningitis:** 2 g x 2 iv or 4 g x 1 iv *S. aureus:* High dose only **Uncomplicated gonorrhoea:** 0.5-1 g im as a single dose
Cefuroxime iv	0.75 g x 3 iv	1.5 g x 3 iv		*S. aureus*: High dose only
Cefuroxime oral	0.25 g x 2 oral	0.5 g x 2 oral	0.25 g x 2 oral	
Piperacillin-tazobactam	(4 g piperacillin + 0.5 g tazobactam x 4 iv 30-minute infusion or x 3 iv by extended 4-hour infusion	g piperacillin + 0.5 g tazobactam x 4 iv by extended 3-hour infusion		A lower dosage of (4 g piperacillin + 0.5 g tazobactam) x 3 iv, 30-minute infusion, is adequate for some infections such as complicated UTI, intraabdominal infections and diabetic foot infections, but not for infections caused by isolates resistant to third-generation cephalosporins.
Doripenem	0.5 g x 3 iv over 1 hour	1 g x 3 iv over 1 hour		HAP/VAP* due to non-fermenting Gram-negative pathogens (such as *Pseudomonas* spp. and *Acinetobacter* spp.) should be treated with 1 g x 3 iv over 4 hours.
Ertapenem	1 g x 1 iv over 30 minutes	None		
Imipenem	0.5 g x 4 iv over 30 minutes	1 g x 4 iv over 30 minutes		
Imipenem-relebactam	(0.5 g imipenem + 0.25 g relebacta x 4 iv over 30 minutes	None		
Meropenem	1 g x 3 iv over 30 minutes	2 g x 3 iv over 3 hours		**Meningitis**: 2 g x 3 iv over 30 minutes (or 3 hours)
Meropenem-vaborbactam	(2 g meropenem + 2 g va	ctam) x 3 iv over 3 hours		

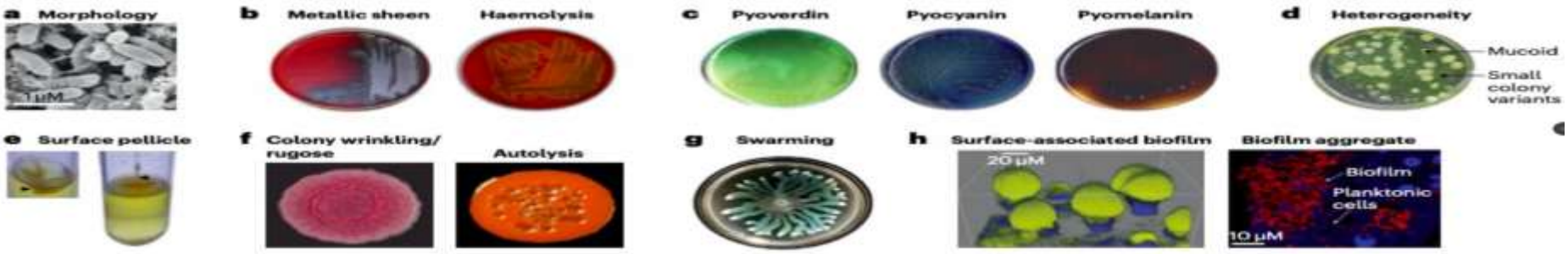
* HAP/VAP = hospital-acquired pneumonia/ventilator-associated pneumonia

Monobactams	Standard dosage	High dosage	Uncomplicated UTI	Special situations
Aztreonam	1 g x 3 iv	2 g x 4 iv		**Severe *P. aeruginosa* infections:** 2 g x 4 with extended 3-hour infusion
Aztreonam-avibactam	(2 g aztreonam followed by (1.5 g aztreonam +	g avibactam) x 1 g avibactam) x 4 iv over 3 hours		

Fluoroquinolones	Standard dosage	High dosage	Uncomplicated UTI	Special situations
Ciprofloxacin	0.5 g x 2 oral or 0.4 g x 2 iv	0.75 g x 2 oral or 0.4 g x 3 iv		**Meningitis:** 0.4 g x 3 iv
Delafloxacin	0.45 g x 2 oral or 0.3 g x 2 iv	None		
Levofloxacin	0.5 g x 1 oral or 0.5 g x 1 iv	0.5 g x 2 oral or 0.5 g x 2 iv		
Moxifloxacin	0.4 g x 1 oral or 0.4 g x 1 iv	None		**Meningitis:** 0.4 g x 1 iv
Norfloxacin	None	None	0.4 g x 2 oral	
Ofloxacin	0.2 g x 2 oral or 0.2 g x 2 iv	0.4 g x 2 oral or 0.4 g x 2 iv		

Aminoglycosides	Standard dosage	High dosage	Uncomplicated UTI	Special situations
Amikacin	25-30 mg/kg x 1 iv	None		
Gentamicin	6-7 mg/kg x 1 iv	None		
Netilmicin	6-7 mg/kg x 1 iv	None		
Tobramycin	6-7 mg/kg x 1 iv	None		





Present and future of resistance in Pseudomonas aeruginosa: implications for treatment. Pina-Sánchez M, Rua M, Del Pozo JL. Rev Esp Quimioter. 2023 Nov;36 Suppl 1(Suppl 1):54-58. doi: 10.37201/req/s01.13.2023. Epub 2023 Nov 24.

Table 3. Major resistance mechanism of *P. aeruginosa* based on antibiotics classes.

	Resistance Mechanisms			
Antibiotic class	Mechanism 1	Mechanism 2	Mechanism 3	Mechanism 4
Beta-lactams	chromosomal AmpC hyper-expression	OprM porin mutation or loss	OXA-1 & -2 enzyme production	MexXY efflux pump overexpression
Aminoglycosides	altered permeability	cytoplasm expression of aminoglycoside-modifying enzymes, such as aminoglycoside-2"-O-nucleotidyltransferase ANT (ANT 2"Ia) and aminoglycoside 4'-O-adenylyltransferase (ANT 4'-IIb	overexpression of MexXY efflux pumps	
Fluoroquinolones	gyrase (gyr A)—topoisomerase expression; (par C) mutations	altered permeability	efflux systems	
Carbapenems	OprD porin loss	MexXY efflux pump expression	beta-lactamase production	

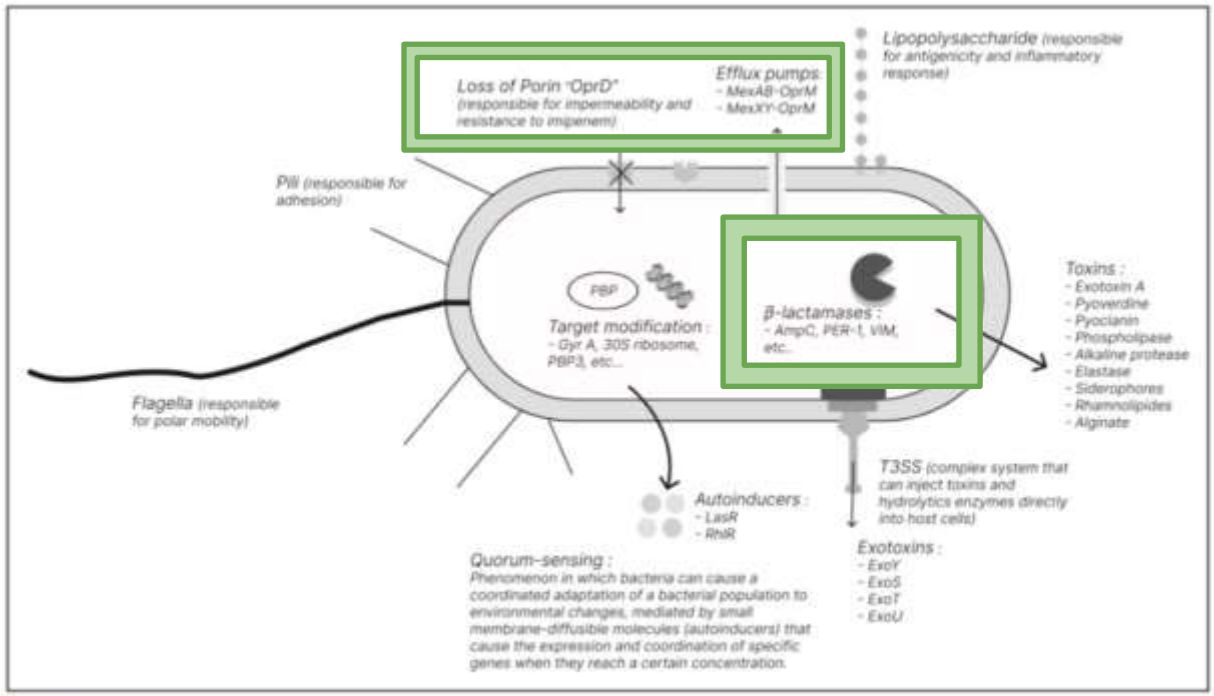


FIGURE 1. Schematic representation of the large number of virulence factors and mechanisms of resistance produced by *P. aeruginosa*.

Management strategies for severe Pseudomonas aeruginosa infections. Do Rego H, Timsit JF. Curr Opin Infect Dis. 2023 Dec 1;36(6):585-595.

Table 1. Risk factors for *P. aeruginosa* infections, with and without antimicrobial resistance

Risk factors for PA infections	Risk factors for resistant PA infections
Underlying illness o Old patients o Severe immune deficiencies o Structural lung disease Medical history o Septic shock o Device usage o Mechanical ventilation o Hemodiaysis o Previous broad-spectrum antibiotic therapy Infections characteristics: o Pneumonia o Catheter-related infections Structural factors o Ecology of the unit o Previous colonization with PA	Structural factors: o Local epidemiology with more than 20% of resistant strains o High colonization pressure in the unit Medical history: o Transfer from long-term healthcare facilities o Previous hospitalization o Previous colonization with resistant PA o History of broad-spectrum (carbapenems and fluoroquinolones) antimicrobial exposure o Number of previous broad-spectrum antimicrobial regimens during the hospitalization o Length of broad-spectrum antimicrobial exposure o Tracheostomy o Central Venous Catheter ports

Management strategies for severe Pseudomonas aeruginosa infections. Do Rego H, Timsit JF. Curr Opin Infect Dis. 2023 Dec 1;36(6):585-595.

Clinical Infectious Diseases
MAJOR ARTICLE

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

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

Comparing efficacy & safety of different monotherapies for definitive treatment of Pseudomonas aeruginosa bacteremia

	30-d mortality	P. aeruginosa with new resistance to antipseudomonal drug
CEFTAZIDIME	17 %	12.4 %
PIP/TAZO	20 %	8.4 %
CARBAPENEMS	16 %	17.5 %
	p 0.48	p 0.007

No significant difference in mortality, clinical & microbiological outcomes between ceftazidime, PIP/TAZO and carbapenems as definitive treatment of P. aeruginosa bacteremia. HIGHER RATES of resistant P. aeruginosa after treatment with carbapenems

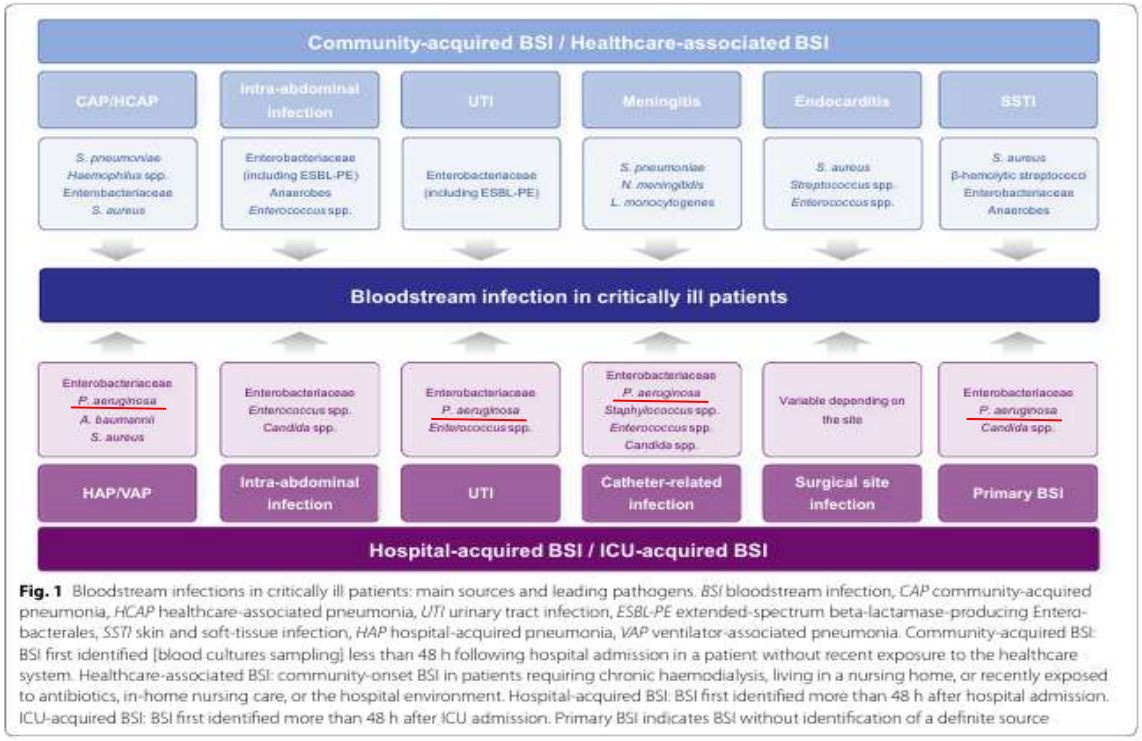


Fig. 1 Bloodstream infections in critically ill patients: main sources and leading pathogens. *BSI* bloodstream infection, *CAP* community-acquired pneumonia, *HCAP* healthcare-associated pneumonia, *UTI* urinary tract infection, *ESBL-PE* extended-spectrum beta-lactamase-producing Enterobacterales, *SSTI* skin and soft-tissue infection, *HAP* hospital-acquired pneumonia, *VAP* ventilator-associated pneumonia. Community-acquired BSI: BSI first identified (blood cultures sampling) less than 48 h following hospital admission in a patient without recent exposure to the healthcare system. Healthcare-associated BSI: community-onset BSI in patients requiring chronic haemodialysis, living in a nursing home, or recently exposed to antibiotics, in-home nursing care, or the hospital environment. Hospital-acquired BSI: BSI first identified more than 48 h after hospital admission. ICU-acquired BSI: BSI first identified more than 48 h after ICU admission. Primary BSI indicates BSI without identification of a definite source

Intensive Care Med 2020 Feb;46(2):266-284. doi: 10.1007/s00134-020-05950-6. Epub 2020 Feb 11. **Bloodstream infections in critically ill patients: an expert statement** Jean-François Timsit et al.

AGENTI EZIOLOGICI DELLE HAP e VAP

Early-onset pneumonia	*Late-onset pneumonia*	*Altri*
Streptococcus pneumoniae	***Pseudomonas aeruginosa***	Anaerobic bacteria
Haemophilus influenzae	***Enterobacter*** spp	***Legionella pneumophila***
Moraxella catarrhalis	***Acinetobacter*** spp	Influenza virus types A e B
Staphylococcus aureus	***Klebsiella pneumoniae***	Respiractory syncytial virus
Aerobic gram-negative bacilli	***Serratia marcescens***	Fungi
	Escherichia coli	
	Other Gram-negative ***bacilli***	
	S. aureus	

QUADRI CLINICI

Infezioni del tratto respiratorio
- pazienti con infezioni croniche (fibrosi cistica)
- infezioni in BPCO
- VAP

Infezioni di ferite chirurgiche
- ustione acute o ulcere croniche
- infezione cute e tessuti molli

Infezioni del torrente circolatorio

Infezioni del tratto urinario
- catetere correlata
- sottostante patologia

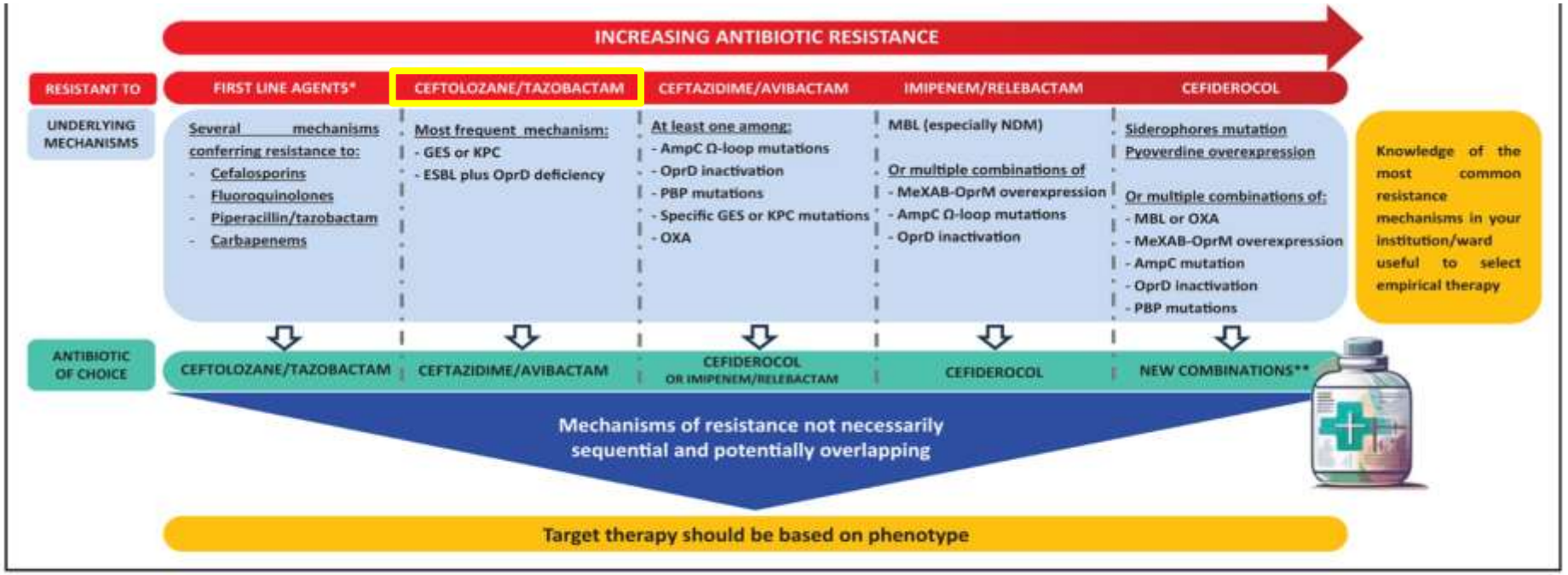
Infezioni dell'occhio
- cheratite attinica dopo chirurgia oculare o lenti/lacrime artificiali contaminate

Skin manifestations of *Pseudomonas aeruginosa*

Infections	Comments
Ecthyma gangrenosum	Immunocompromised (e.g. neutropenia), gangrenous ulcers, progress rapidly (within 12 hours), **hemorrhagic necrosis**
Burn wound	One of the most commonly isolated organisms from burn patients**, approximately 60%**
Nail puncture injury	The moist inner sole of the shoe **(suitable environment for growth)**
Hot tub folliculitis	**Benign, self-limited skin lesions**, following exposure to contaminated water
Toe web infection	Associated with the use of **closed-toe or tight-fitting shoes,** often bilateral
Green nail syndrome	Complication of **onycholysis or chronic paronychia**, usually one or two nails
Perichondritis	Following **ear piercing or acupuncture**
External otitis	Acute, malignant, Advanced age, **diabetes** mellitus and immunosuppression

P. aeruginosa can cause various specific clinical skin and soft tissue infections along with common infections such as surgical site infections, chronic decubitus ulcers, infections following trauma.

Curr Opin Infect Dis. 2021 Apr 1;34(2):72-79, Dermatol Online J. 2016;22(1) Epub 2016 Jan 15.
Am J Med. 1981;70(5):1133, UpToDate: *Pseudomonas aeruginosa* skin and soft tissue infections



Scenarios of antibiotic resistance in *Pseudomonas aeruginosa* and underling mechanisms. *Resistance to: cefalosporins, fluoroquinolones, piperacillin/tazobactam, carbapenems (contemporary presence defines DTR-PA). **Cefepime/zidebactam, cefepime/taniborbactam, aztreonam/avibactam. MBL, metallo-β-lactamases; PBP, nonessential penicillin binding protein.

Not all carbapenem-resistant Pseudomonas aeruginosa strains are alike: tailoring antibiotic therapy based on resistance mechanisms Falcone, Marco; Galfo, Valentina; Tiseo, Giusy *Current Opinion in Infectious Diseases* 37(6):p 594-601, December 2024.

CEFTOLOZANE TAZOBACTAM

26-1-2021 GAZZETTA UFFICIALE DELLA REPUBBLICA ITALIANA Serie generale - n. 20

Scheda cartacea per la prescrizione della specialità medicinale ZERBAXA (ceftolozano-tazobactam)

Indicazioni terapeutiche: Zerbaxa è indicato per il trattamento delle seguenti infezioni negli adulti:

- Infezioni intra-addominali complicate
- Pielonefrite acuta
- Infezioni complicate del tratto urinario
- Polmonite acquisita in ospedale (HAP), inclusa la polmonite associata a ventilazione meccanica (VAP)

Devono essere considerate le linee guida ufficiali sull'uso appropriato degli agenti antibatterici.

Azienda Sanitaria: _____

Unità Operativa Richiedente: _____ Data: ___/___/____

Paziente (nome, cognome): _____ Data di nascita: ___/___/____

Sesso: F ☐ M ☐ Codice Fiscale o Tessera Sanitaria dell'Assistito: _____

La rimborsabilità è limitata alla pielonefrite acuta, alle infezioni complicate del tratto urinario sostenute da batteri gram-negativi resistenti ai trattamenti di prima linea, alle infezioni addominali complicate e alle polmoniti acquisite in ospedale (HAP), incluse le polmoniti associate a ventilazione meccanica (VAP), la cui eziologia documentata o sospetta è dovuta a batteri gram-negativi resistenti ai trattamenti di prima linea.

Diagnosi	
Infezione intra-addominale complicata (cIAI) con eziologia documentata/sospetta* da batteri Gram-negativi, resistente ai trattamenti di prima linea (se si sospetta la presenza di patogeni anaerobi Zerbaxa dovrà essere associato a metronidazolo)	☐
Infezione complicata del tratto urinario (cUTI), inclusa la pielonefrite acuta, con eziologia documentata da batteri Gram-negativi resistenti ai trattamenti di prima linea (Allegare antibiogramma)	☐
Polmonite acquisita in ospedale (HAP), inclusa la polmonite associata a ventilazione meccanica (VAP), con eziologia documentata/sospetta* da batteri Gram-negativi resistenti ai trattamenti di prima linea (da usare in associazione con un agente attivo antibatterico nei confronti di patogeni Gram-positivi, quando questi sono noti o sospetti nel contribuire al processo infettivo)	☐
*L'infezione "sospetta" può essere considerata in pazienti selezionati sulla base di criteri epidemiologici, clinici e microbiologici (ad es. colonizzazione intestinale) in accordo a raccomandazioni terapeutiche definite dal programma di stewardship antibiotica del singolo ospedale.	

PROGRAMMA TERAPEUTICO

Farmaco	Specialità	Dose	Durata prevista
Zerbaxa	1g./0,5g. polvere per concentrato per soluzione per infusione		

Il dosaggio standard in soggetti con CrCl>50 mL/min è 1 g. ceftolozano/0,5 g. tazobactam ogni 8 ore (tempo di infusione: 1 h.) per una durata di 4-14 giorni nel trattamento delle cIAI e di 7 giorni nel trattamento della pielonefrite acuta e delle cUTI. Nelle HAP/VAP il dosaggio è pari a 2g./1g. ogni 8 ore (tempo di infusione: 1 h.) per una durata di 8-14 giorni.

Spettro di azione

Gram pos
- streptococci compreso pneumoniae (MIC 4)

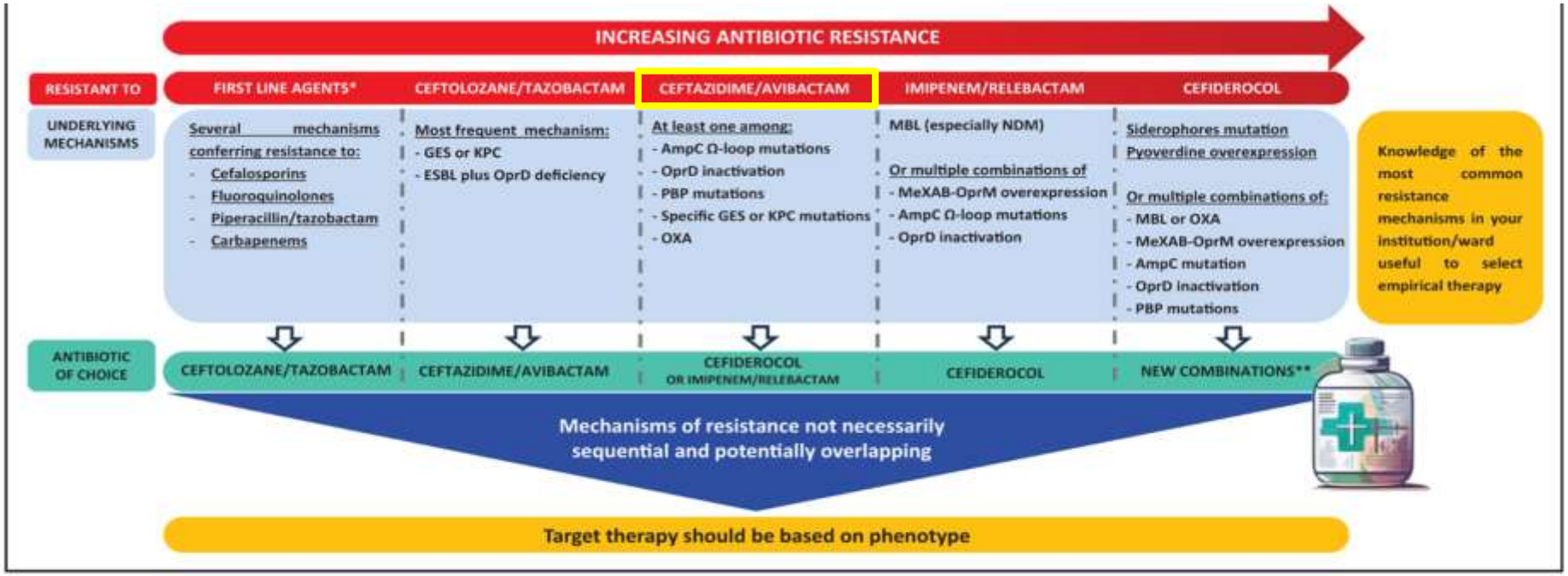
Gram neg
- Enterobacteriaceae inclusa ESBL (no OXA 48 e GES)
- proteus e serratia KPC o no
- P. aeruginosa (MIC 2). AmpC.
- Burkholderia pseudomallei 50% cepacia

Anaerobi
- fusobacterium, prevotella, cutibacterium acnes, c. perfrigens e batterioides fragilis

ASPECT-cUTI cef-tazobactam 1.5 ogni 8 h superiore a levofloxacina 750 mg per 7 gg

ASPECT-cIAI c/t + metronidazolo non inferiore a meropenem durata 4-14 gg

ASPECT-NP (VAP/HAP) c/t vs meropenem non inferiorità a 28 gg come mortalità e outcome clinico



Scenarios of antibiotic resistance in *Pseudomonas aeruginosa* and underling mechanisms. *Resistance to: cefalosporins, fluoroquinolones, piperacillin/tazobactam, carbapenems (contemporary presence defines DTR-PA). **Cefepime/zidebactam, cefepime/taniborbactam, aztreonam/avibactam. MBL, metallo-β-lactamases; PBP, nonessential penicillin binding protein.

Antibiotico	*Pseudomonas aeruginosa*			
	AmpC	Pompe d'efflusso	Perdita di porine	IMP/VIM/NDM
Ceftolozano/tazobactam				
Ceftazidime/avibactam				
Meropenem/vaborbactam				
Imipenem/Relebactam				
Aztreonam/avibactam				
Cefiderocol				
Plazomicina				
Eravaciclina				

Not all carbapenem-resistant Pseudomonas aeruginosa strains are alike: tailoring antibiotic therapy based on resistance mechanisms Falcone, Marco; Galfo, Valentina; Tiseo, Giusy *Current Opinion in Infectious Diseases* 37(6):p 594-601, December 2024.

CEFTAZIDIME AVIBACTAM

Diagnosi	
Infezione complicata del tratto urinario (cUTI), incluse le pielonefriti, con eziologia documentata da batteri Gram-negativi resistenti ai trattamenti di prima linea (Allegare antibiogramma)	☐
Infezione intra-addominale complicata (cIAI) con eziologia documentata/sospetta* da batteri Gram-negativi, resistente ai trattamenti di prima linea)	☐
Polmonite acquisita in ospedale (HAP), inclusa polmonite associata a ventilazione meccanica (VAP), con eziologia documentata/sospetta* da batteri Gram-negativi, resistente ai trattamenti di prima linea	☐
Infezioni causate da microrganismi Gram-negativi aerobi in pazienti adulti nei quali vi siano opzioni terapeutiche limitate, con eziologia documentata/sospetta* da batteri Gram-negativi, resistente ai trattamenti di prima linea	☐
*L'infezione "sospetta" può essere considerata in pazienti selezionati sulla base di criteri epidemiologici, clinici e microbiologici (ad es. colonizzazione intestinale) in accordo a raccomandazioni terapeutiche definite dal programma di stewardship antibiotica del singolo ospedale.	

PROGRAMMA TERAPEUTICO

Farmaco	Specialità	Dose	Durata prevista (cfr. RCP)
Zavicefta	2g./0,1g. polvere per concentrato per soluzione per infusione	2g. ceftazidima/0,5g. avibactam ogni 8 ore	

Il dosaggio standard in soggetti con CrCl>50 mL/min è 2 g. ceftazidima/0,5 g. avibactam ogni 8 ore (tempo di infusione: 2 h.) per una durata di 5-14 giorni nel trattamento delle cIAI, di 5-10 giorni nel trattamento delle cUTI (inclusa la pielonefrite acuta) e di 7-14 giorni per le polmoniti acquisite in ospedale (incluse le VAP). Vi è esperienza molto limitata per un utilizzo superiore a 14 giorni

	Ceftolozane–tazobactam group	Ceftazidime–avibactam group	Unadjusted OR (95% CI)	Unadjusted p value	Adjusted OR* (95% CI)	Adjusted p value
All patients (n=420)						
Clinical success	128 (61%)	109 (52%)	1·50 (1·00–2·26)	0·053	2·07 (1·16–3·70)	0·013
30-day mortality	48 (23%)	50 (24%)	0·94 (0·59–1·51)	0·81	0·77 (0·41–1·53)	0·49
90-day mortality	79 (38%)	77 (37%)	1·04 (0·70–1·56)	0·84	0·95 (0·56–1·61)	0·86
Recurrence within 30 days	31 (15%)	44 (21%)	0·65 (0·39–1·09)	0·099	0·50 (0·25–0·99)	0·048
Recurrence within 90 days	53 (25%)	65 (31%)	0·73 (0·47–1·15)	0·18	0·62 (0·34–1·11)	0·11
Emergence of resistance†	38 (22%)	40 (23%)	0·96 (0·58–1·60)	0·89	0·95 (0·56–1·63)	0·86
Pneumonia subgroup (n=350)						
Clinical success	110 (63%)	89 (51%)	1·68 (1·08–2·62)	0·022	2·34 (1·23–4·47)	0·0098
30-day mortality	39 (22%)	41 (23%)	0·93 (0·56–1·56)	0·79	0·97 (0·49–1·94)	0·95
90-day mortality	59 (34%)	66 (38%)	0·84 (0·55–1·30)	0·44	0·81 (0·46–1·42)	0·45
Recurrence within 30 days	26 (15%)	40 (23%)	0·58 (0·33–1·01)	0·055	0·44 (0·20–0·97)	0·041
Recurrence within 90 days	45 (26%)	61 (35%)	0·62 (0·38–1·01)	0·055	0·48 (0·24–0·94)	0·033
Emergence of resistance†	30 (21%)	37 (26%)	0·78 (0·45–1·35)	0·38	0·75 (0·42–1·35)	0·34

OR is presented using the ceftolozane–tazobactam cohort as the reference such that an OR greater than 1 corresponds to a greater odds of the outcome for patients who received ceftolozane–tazobactam and an OR less than 1 corresponds to lower odds of the outcome for patients who received ceftolozane–tazobactam. OR=odds ratio. *Controlled for age (≥65 years or <65 years), immunocompromising conditions, infection site, suboptimal dosing, Sequential Organ Failure Assessment score (≥8 or <8), Charlson Comorbidity Index (≥5 or <5), time to treatment initiation, concomitant infections, prolonged infusions, and receipt of renal replacement therapy using conditional logistic regression analyses. For the overall cohort, infection site was also included, but not for the pneumonia subgroup. †Based on the number of patients whose baseline isolates were confirmed to be susceptible by the local study site testing methods (n=173 for ceftolozane–tazobactam and n=177 for ceftazidime–avibactam overall; n=144 for ceftolozane-tazobactam and n=147 for ceftazidime-avibactam in the pneumonia subgroup).

Table 2: **Primary and select secondary outcomes among all patients and patients with pneumonia**

Spettro di azione

Gram neg

- Enterobacteriaceae incluse ESBL e KPC (MIC 8/4)
- proteus e serratia KPC o no
- P. aeruginosa (MIC 2). NO mutazione AmpC.
- Burkholderia cepacia
- acinetobacter e achromobacter

- M. abscessus e tb

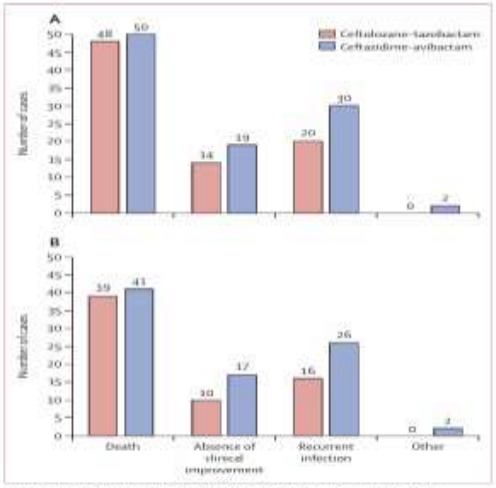


Figure 2: **Reasons for clinical failure of treatment at 30 days across all patients (A) and those with pneumonia specifically (B)**
There were a total of 210 patients (A) and 175 patients (B) in each treatment group. Reasons for clinical failure are shown as one per patient; however, patients might have had multiple reasons for failure. For example, among patients with absence of clinical improvement, 29% (four of 14 patients) and 47% (nine of 19 patients) also had recurrent infections within 30 days of treatment with ceftolozane–tazobactam and ceftazidime–avibactam, respectively. The corresponding proportions among patients with pneumonia specifically were 40% (four of ten patients) and 47% (eight of 17 patients), respectively. Other reasons for failure included drug discontinuation due to hypersensitivity reactions in two patients.

Effectiveness of ceftazidime–avibactam versus ceftolozane–tazobactam for multidrug-resistant *Pseudomonas aeruginosa* infections in the USA (CACTUS): a multicentre, retrospective, observational study

MBL producing *P. aeruginosa*

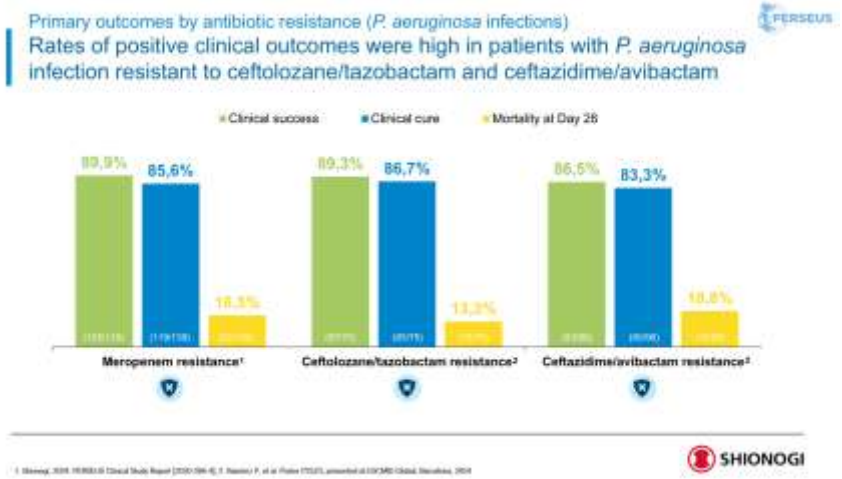
A recent systematic review of *in vitro* and clinical cases reported that ATM + AVI did not show synergy in *P. aeruginosa* isolates, leading to the conclusion that:

- data did not support clinical decisions for use of CAZ/AVI + ATM for treatment of MBL-producing *P. aeruginosa* (n=772)
- >90% of *P. aeruginosa* isolates had MIC values ≥16 mg/L
- *In vitro* activity of CAZ/AVI + ATM *in P. aeruginosa* susceptibility rates: 6%

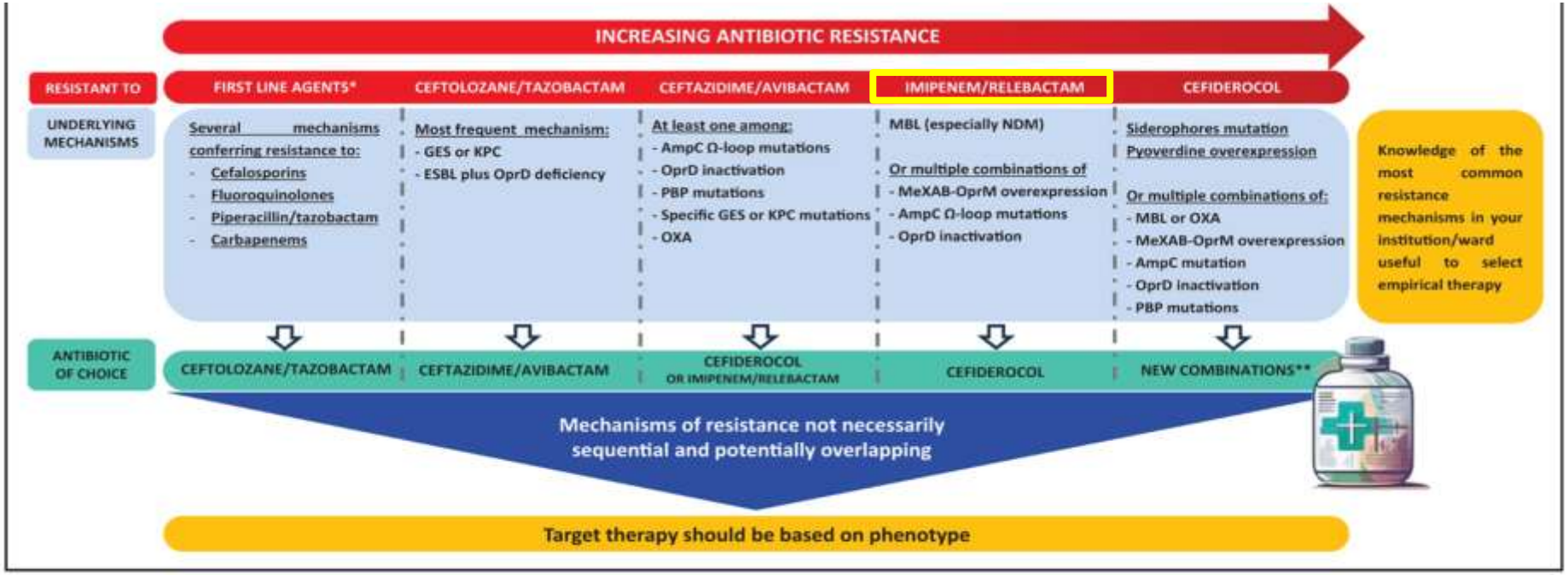
Mauri C, et al. *Antibiotics* (Basel). 2021;10:1012.

Effectiveness of ceftazidime–avibactam versus ceftolozane–tazobactam for multidrug-resistant *Pseudomonas aeruginosa* infections in the USA (CACTUS): a multicentre, retrospective, observational study

11%-14% treatment emergent resistance has been reported
after patient were treated with C/T



Haidar et al. Clin Infect Dis 2017
Diaz –Canestro et al. Eur J Clin Microbiol Infect Dis 2018
Fraile-Ribot et al. J Antimicrob Chemother 2018



Scenarios of antibiotic resistance in *Pseudomonas aeruginosa* and underling mechanisms. *Resistance to: cefalosporins, fluoroquinolones, piperacillin/tazobactam, carbapenems (contemporary presence defines DTR-PA). **Cefepime/zidebactam, cefepime/taniborbactam, aztreonam/avibactam. MBL, metallo-β-lactamases; PBP, nonessential penicillin binding protein.

Antibiotico	*Pseudomonas aeruginosa*			
	AmpC	Pompe d'efflusso	Perdita di porine	IMP/VIM/NDM
Ceftolozano/tazobactam				
Ceftazidime/avibactam				
Meropenem/Vaborbactam				
Imipenem/Relebactam				
Aztreonam/avibactam				
Cefiderocol				
Plazomicina				
Eravaciclina				

Not all carbapenem-resistant Pseudomonas aeruginosa strains are alike: tailoring antibiotic therapy based on resistance mechanisms Falcone, Marco; Galfo, Valentina; Tiseo, Giusy *Current Opinion in Infectious Diseases* 37(6):p 594-601, December 2024.

IMIPENEM RELEBACTAM

Diagnosi	
• *Infezioni gravi causate da batteri Gram-negativi con resistenza ai carbapenemi documentata dall'antibiogramma in assenza di altre opzioni terapeutiche*	☐
• *Infezioni gravi/invasive con resistenza ai carbapenemi fortemente sospetta in caso di almeno una delle seguenti condizioni:*	☐
○ *documentata colonizzazione da Gram-negativi con resistenza ai carbapenemi*	☐
○ *documentata endemia da batteri Gram-negativi resistenti ai carbapenemi nell'U.O. richiedente*	☐
*In caso di infezione documentata indicare l'agente eziologico:*_____	

PROGRAMMA TERAPEUTICO

Farmaco	Specialità	Dose	Durata prevista (cfr. RCP)
Recarbrio	2g. polvere per concentrato per soluzione per infusione	500 mg/500 mg/250 mg ogni 6 ore [1]	In base alla sede dell'infezione [2]

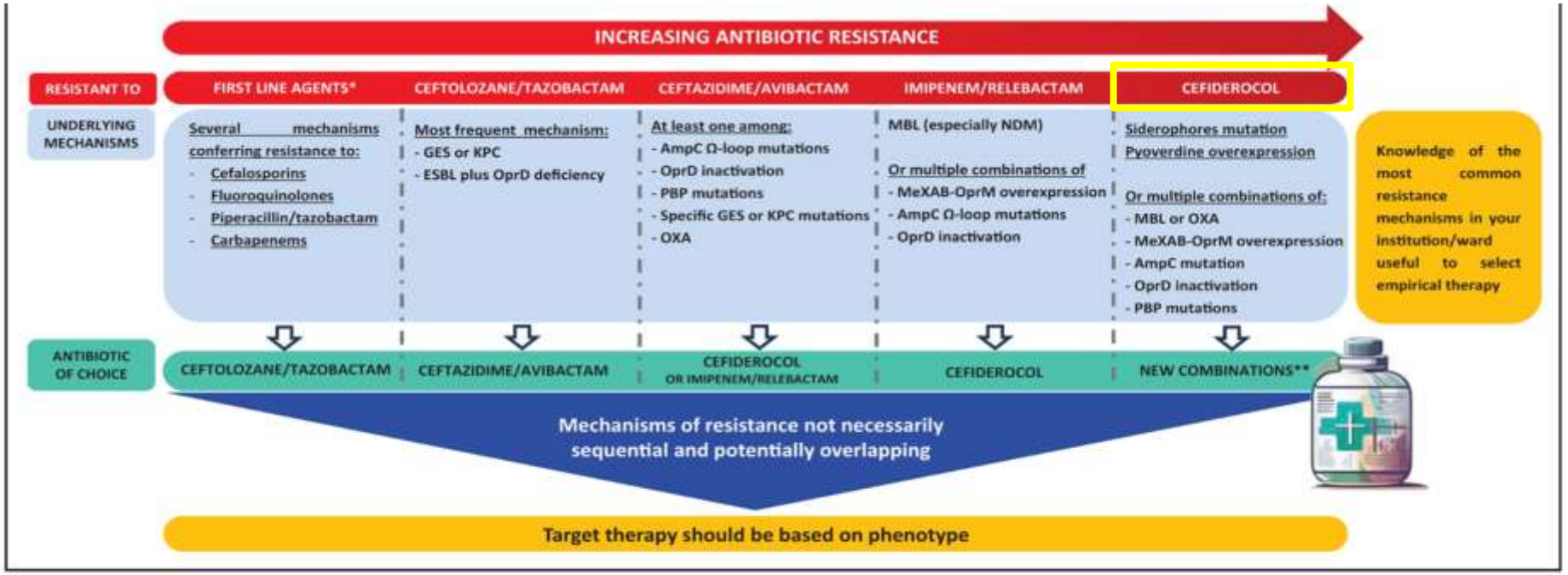
[1] Per pazienti con una clearance della creatinina (CrCl) da ≥ 90 a < 150 mL/min calcolata utilizzando la formula di Cockcroft-Gault. [2]Ad esempio, per le infezioni complicate del tratto urinario (cUTI), compresa la pielonefrite e per le infezioni intra-addominali complicate (cIAI) la durata raccomandata del trattamento è da 5 a 10 giorni; il trattamento può proseguire fino a 14 giorni. Per la polmonite acquisita in ospedale/polmonite associata a ventilazione meccanica (HAP/VAP) la durata raccomandata del trattamento è da 7 a 14 giorni.
Sono previsti aggiustamenti di dose in relazione della funzionalità renale (cfr. RCP del prodotto)

<u>Spettro di azione</u>

Gram neg
- Enterobacteriaceae inclusa KPC (no OXA 48 e GES)
- Proteus e Serratia KPC o no
- 80% P. aeruginosa (MIC 2:8). NO MBL

RESTORE-IMI 1 imipenem relebactam vs colistina + imipenem .
Efficacia comparabile, meno effetti collaterali

RESTORE-IMI 2 imipenem rel vs pip-tazobactam in HAP/VAP.
Mortalità e risposta clinica a 28 gg a favore di imi-rel-cilastatina



Scenarios of antibiotic resistance in *Pseudomonas aeruginosa* and underling mechanisms. *Resistance to: cefalosporins, fluoroquinolones, piperacillin/tazobactam, carbapenems (contemporary presence defines DTR-PA). **Cefepime/zidebactam, cefepime/taniborbactam, aztreonam/avibactam. MBL, metallo-β-lactamases; PBP, nonessential penicillin binding protein.

Antibiotico	*Pseudomonas aeruginosa*			
	AmpC	Pompe d'efflusso	Perdita di porine	IMP/VIM/NDM
Ceftolozano/tazobactam				
Ceftazidime/avibactam				
Meropenem/Vaborbactam				
Imipenem/Relebactam				
Aztreonam/avibactam				
Cefiderocol				
Piazomicina				
Eravaciclina				

Not all carbapenem-resistant Pseudomonas aeruginosa strains are alike: tailoring antibiotic therapy based on resistance mechanisms Falcone, Marco; Galfo, Valentina; Tiseo, Giusy *Current Opinion in Infectious Diseases* 37(6):p 594-601, December 2024.

CEFIDEROCOL

Diagnosi	
• Infezioni gravi causate da batteri Gram-negativi con resistenza ai carbapenemi documentata dall'antibiogramma in assenza di altre opzioni terapeutiche	☐
• Infezioni gravi/invasive con resistenza ai carbapenemi fortemente sospetta in caso di almeno una delle seguenti condizioni:	☐
○ fallimento di un precedente trattamento con carbapenemi (in dosi/durata appropriata)	☐
○ documentata colonizzazione da Gram-negativi con resistenza ai carbapenemi	☐
○ documentata endemia da batteri Gram-negativi resistenti ai carbapenemi nell'U.O. richiedente	☐
In caso di infezione documentata indicare l'agente eziologico:_____	

PROGRAMMA TERAPEUTICO

Farmaco	Specialità	Dose	Durata prevista (cfr. RCP)
Cefiderocol	Fetcroja 1g polvere per concentrato per soluzione per infusione	2g ogni 8 ore	In base alla sede dell'infezione [1]

[1] Per le infezioni complicate delle vie urinarie, inclusa pielonefrite, e le infezioni intra-addominali complicate la durata del trattamento raccomandata è compresa tra 5 e 10 giorni. Per la polmonite nosocomiale, inclusa la polmonite associata a ventilazione, la durata del trattamento raccomandata è compresa tra 7 e 14 giorni. Può essere richiesto un trattamento fino a 21 giorni.
Sono previsti aggiustamenti di dose in relazione della funzionalità renale (cfr. RCP del prodotto)

Spettro di azione

Gram pos
- s. pneumoniae

Gram neg
- Enterobacteriaceae incluse ESBL, KPC, MBL
- P. aeruginosa (MIC 2:8). NO MBL
- B. cepaci, pseudomallei, s. maltophilia
- Neisseria, moraxella, bordetella

Anaerobi
- Fusobacterium necrophorum e c. perfrigens.

APEKS-NP HAP/VAP cefiderocol vs meropenem . Efficacia comparabile, meno effetti collaterali

CREDIBLE - CR hap/bsi/cUTI da CR GNB

Real- World use of cefiderocol in the EU and US for *P. Aeruginosa*: interim data from the PROVE study – poster 2274

Baseline characteristics of patients

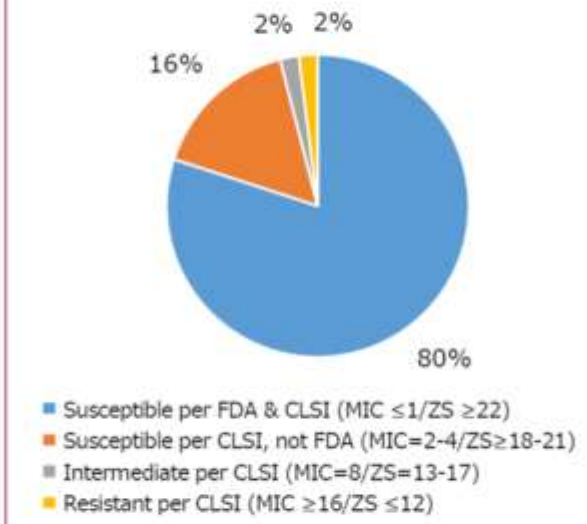
- 194 patients in PROVE were identified with PA as of November 1, 2022, the first having been sampled May 1, 2021. 191 were primary site pathogens for which cefiderocol was prescribed.

Infection sites, pathogens, and antimicrobial susceptibility

- Monomicrobial infections accounted for most (67.5%) of the primary infections (N=191; **Figure 1**). Respiratory and bloodstream infections (BSIs) accounted for 76.4% (146/191) of all primary infections.
- MIC or zone size was available for 107 primary PA infections. EUCAST breakpoints for cefiderocol susceptibility (MIC ≤2 µg/mL or zone size ≥22 mm) classified 91.6% (98/107) as susceptible. Applying FDA and CLSI breakpoints, 96.3% (CLSI) and 80% (FDA) were susceptible **(Figure 2)**.

Figure 1. Primary sites of infection

Figure 2. PA susceptibility (FDA and CLSI) to cefiderocol (n=107)[a]



[a]Also includes the non-primary PA cultures (N=4).
ZS, zone size

[b]Refers to secondary bacteremia with another primary site of infection.

PROVE study: clinical outcomes

Table 3. Outcomes by key characteristics (n=191)

	Overall		Clinical cure[b]		30-day post-CFDC mortality	
	n	%	n	Row%	n	Row%
Number of patients[a]	191	100%	124	64.9%	37	19.4%

Clinical outcomes

- Overall, 64.9% of patients achieved clinical cure without relapse and 30-day ACM was 19.4% (**Table 3**). Similar cure rates were observed in patients with monomicrobial and polymicrobial infections.
- Respiratory site accounted for the majority of infections, with cure rates of 60.8% and 71.0%, respectively for monomicrobial and polymicrobial infections.
- Patients with monomicrobial BSI (alone or as secondary bacteremia) (n=31) had a combined cure rate of 67.7% and a 30-day ACM of 22.6%.
  - **Clinical cure was greatest for empiric treatment and documented infections:** 73.3% (95% CI, 44.9%–92.2%) and 68.0% (95% CI, 59.8%–75.5%), respectively.
  - **Clinical cure was lowest for salvage treatment after failure of a prior Gram-negative antibiotic:** 42.3% (95%CI, 23.4%–63.1%).
  - **Clinical cure was greater for monotherapy than for combination therapy:** 74.3% (95% CI, 65.1%–82.2%) vs. 52.4% (95% CI, 41.1%–63.6%).
  - **30-day ACM was lower for empiric therapy than for documented pathogen therapy:** 6.7% (95% CI, 0.17%–31.9%) vs. 19.7% (95% CI, 13.6–27.1).
  - **30-day ACM was lower for monotherapy than for combination therapy:** 12.8% (95% CI, 7.2%–20.6%) vs. 28.1% (95% CI, 18.7%–39.1%).

Real- World use of cefiderocol in the EU and US for *P. Aeruginosa*: interim data from the PROVE study – poster 2274

PROVE study: clinical severity of patients during treatments

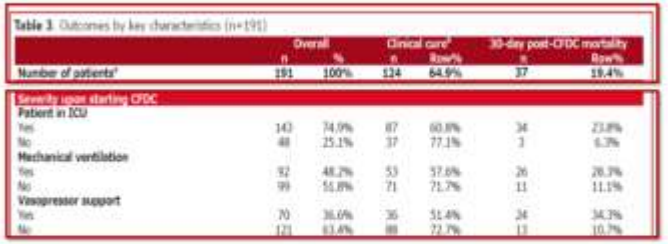
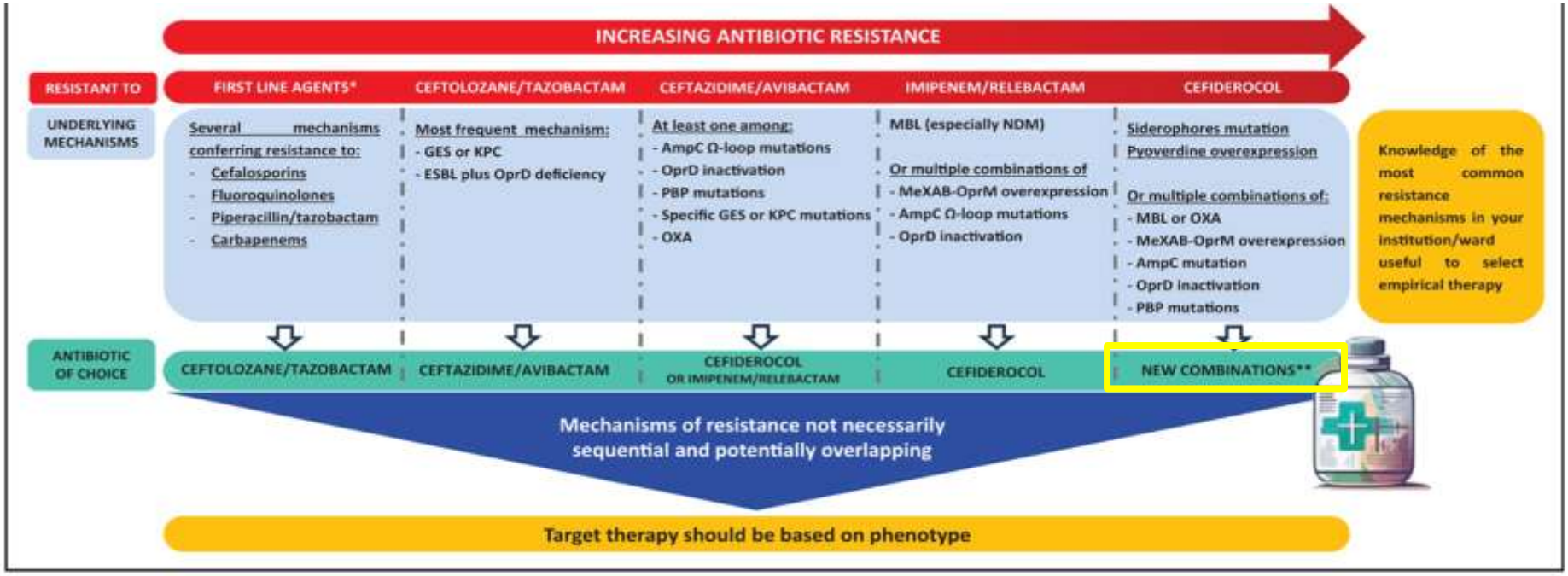


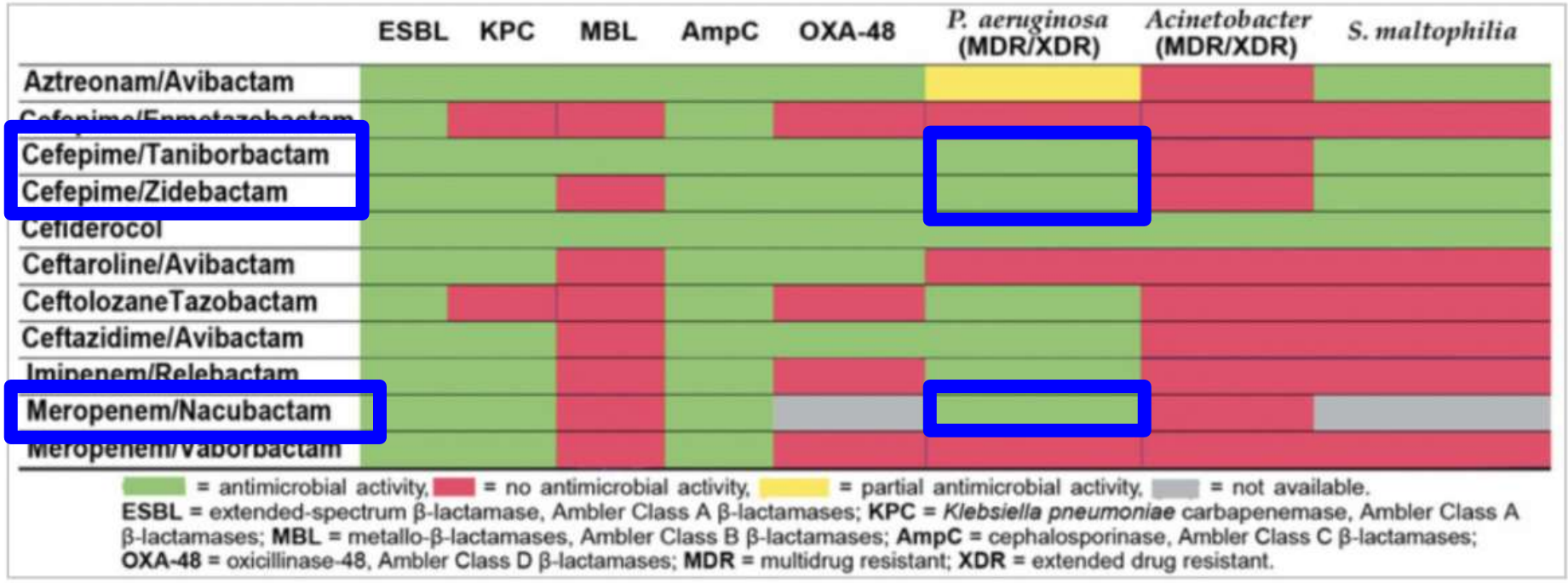
Table 3. Outcomes by key characteristics (n=191)

	Overall		Clinical cure[b]		30-day post-CFDC mortality	
	n	%	n	Row%	n	Row%
Number of patients[a]	191	100%	124	64.9%	37	19.4%
Severity upon starting CFDC						
Patient in ICU						
Yes	143	74.9%	87	60.8%	34	23.8%
No	48	25.1%	37	77.1%	3	6.3%
Mechanical ventilation						
Yes	92	48.2%	53	57.6%	26	28.3%
No	99	51.8%	71	71.7%	11	11.1%
Vasopressor support						
Yes	70	36.6%	36	51.4%	24	34.3%
No	121	63.4%	88	72.7%	13	10.7%

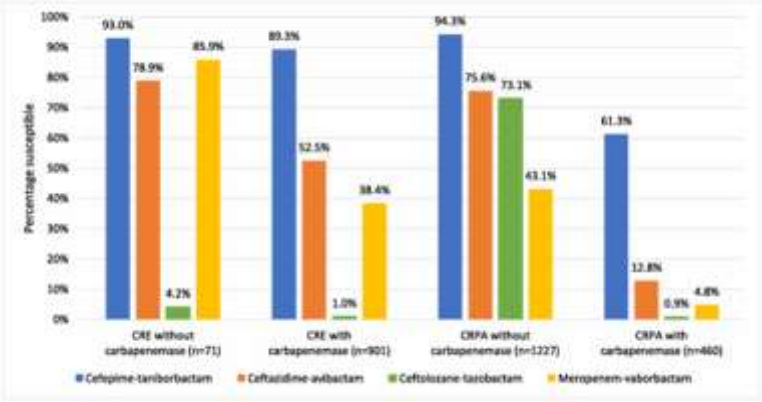
Real- World use of cefiderocol in the EU and US for *P. Aeruginosa*: interim data from the PROVE study – poster 2274



Scenarios of antibiotic resistance in *Pseudomonas aeruginosa* and underling mechanisms. *Resistance to: cefalosporins, fluoroquinolones, piperacillin/tazobactam, carbapenems (contemporary presence defines DTR-PA). **Cefepime/zidebactam, cefepime/taniborbactam, aztreonam/avibactam. MBL, metallo-β-lactamases; PBP, nonessential penicillin binding protein.



CEFEPIME TANIBORBACTAM



Cefepime–taniborbactam activity against antimicrobial-resistant clinical isolates of Enterobacterales and *Pseudomonas aeruginosa*: GEARS global surveillance programme 2018–22
James A Karlowsky , Mark G Wise , Meredith A Hackel , David A Six , Tsuyoshi Uehara , Denis M Daigle , Daniel C Pevear , Greg Moeck , Daniel F Sahm*Journal of Antimicrobial Chemotherapy*, Volume 79, Issue 12, Dec 2024

Spettro di azione

Gram pos
- come cefepime

Gram neg
- Enterobacteriaceae incluse ESBL, KPC, MBL, NDM no IMP
- 80% P. aeruginosa resistenti a cefepime, meropenem, caz/avi, C/T.
- S. maltophilia taniborbactam riduce la MIC del cefepime di 4-8 vv

Anaerobi
- assente come cefepime

Studio fase 3 cUTI: superiore a meropenem

PSEUDOMONAS DTR			
SEPSI E SHOCK SETTICO POLMONITI, INFEZIONI ADDOMINALI CON BONIFICA DEL SITO INFETTIVO NON OTTIMALE, INFEZIONI DEL SNC		**Dosaggio**	**Note**
Prima scelta	**Ceftolozano-tazobactam**	3 g EV q8h	
Seconda scelta	**Ceftazidime-avibactam**	2,5 g EV q8h	
	Imipenem-cilastatina-relebactam	1,25 g EV q6h	
Alternative *se prima e seconda scelta non possibili*	**Cefiderocol**	2 g EV q8h	Infezioni urinarie gravi e infezioni polmonari con documentata produzione di metallo-beta- lattamasi
	Colistina	Dose da carico 9 mln UI EV seguita da 4,5 mln UI EV q12h Terapia intratecale: 125000 UI di colistimetato sodico	Solo in combinazione; nelle meningiti e ventricoliti associare terapia intratecale a quella endovenosa

Table 2 Plasma and epithelial lining fluid concentrations of β-lactam/β-lactamase inhibitor combination products in healthy subjects

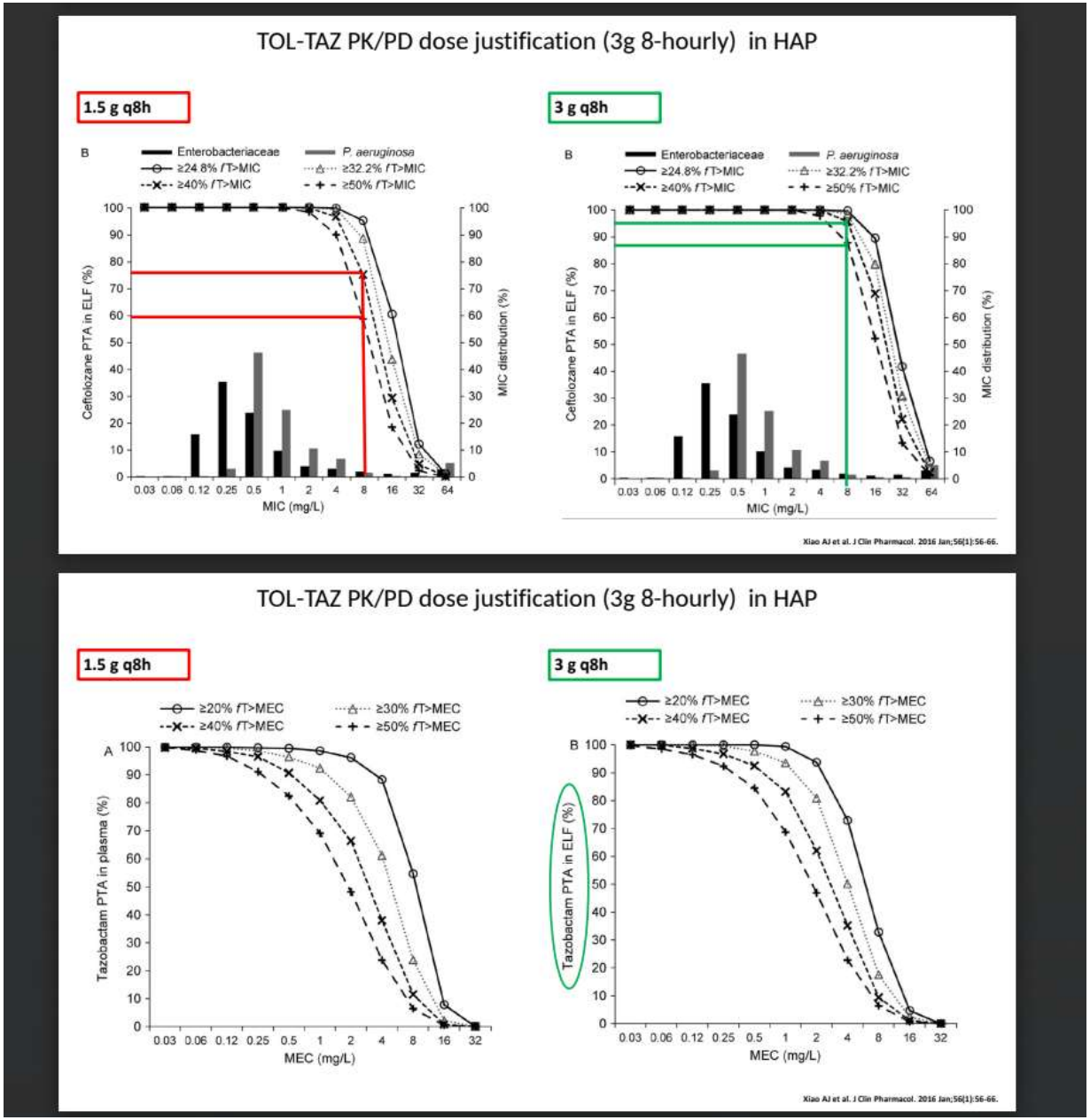
Antibacterial agent	Dosage regimen	Subjects [*n*]	Sampling time [h][a]	Ratio of ELF to plasma based on AUC	Plasma concentration [μg/mL][b]	ELF concentration [μg/mL][b]	References
Piperacillin/ tazobactam	Piperacillin 4 g IV q6h × 3 doses	5	0.5	0.26[c]	263 ± 45	58.8 ± 12.5	[19]
		5	1		152 ± 24	31.0 ± 10.9	
		5	2		69.5 ± 19.8	19.7 ± 9.5	
		5	4		14.8 ± 6.0	6.4 ± 4.5	
		5	6		3.4 ± 1.1	3.0 ± 1.0	
	Tazobactam 0.5 g IV q6h × 3 doses	5	0.5	0.54[c]	29.9 ± 6.1	15.3 ± 7.8	
		5	1		19.0 ± 2.6	7.2 ± 2.8	
		5	2		9.6 ± 2.4	5.2 ± 3.2	
		5	4		1.9 ± 2.4	1.8 ± 1.2	
		5	6		0.7 ± 0.2	1.0 ± 1.0	

SUMMARY OF THE STUDIES INVESTIGATING LUNG PENETRATION OF NOVEL BETA-LACTAMS

Study reference	Selected beta-lactam/Dosage	Setting	No. of patients	$AUC_{ELF/plasma}$ ratio	$C_{max\ ELF/plasma}$ ratio	$T_{max\ ELF/plasma}$ ratio	$t_{1/2\ ELF/plasma}$ ratio	PK/PD target in ELF
Nicolau *et al.*, 2015 [82]	Ceftazidime-avibactam 2000 mg/500 mg q8h (N = 22) 3000 mg/1000 mg q8h (N = 21)	Healthy adult subjects	43	0.31–0.32 (ceftazidime) 0.32–0.35 (avibactam)	0.26 (ceftazidime) 0.35 (avibactam)	1.00 (ceftazidime) 1.00 (avibactam)	1.32 (ceftazidime) 0.59 (avibactam)	Not assessed
Wenzler *et al.* 2015 [83]	Meropenem-vaborbactam 2 g/2 g q8h (infusion in 3-h)	Healthy adult subjects	25	Total concentrations: 0.63 (meropenem) 0.53 (vaborbactam) Unbound fraction: 0.65 (meropenem) 0.79 (vaborbactam)	NA	NA	NA	Not assessed
Rizk *et al.* 2018 [81]	Imipenem-relebactam 500 mg/250 mg q6h	Healthy adult subjects	16	0.55 (imipenem) 0.54 (relebactam)	0.33 (imipenem) 0.32 (relebactam)	1.00 (imipenem) 1.00 (relebactam)	1.08 (imipenem) 1.04 (relebactam)	Not assessed
Katsube *et al.* 2019 [79]	Cefiderocol 2000 mg single dose (1-h infusion)	Healthy adult subjects	15	Total concentrations: 0.10 (ELF) 0.017 (AM) Unbound fraction: 0.24 (ELF) 0.042 (AM)	0.10 (ELF) 0.01 (AM)	1.00 (ELF) 6.00 (AM)	0.98 (ELF) NA (AM)	Not assessed

AM: alveolar macrophages; AUC; area under the time-to-concentration curve; C_{max}: peak concentration; ELF: epithelial lining fluid; HAP: hospital-acquired pneumonia; NA: not assessed; T_{max}: time of peak concentration observed; $t_{1/2}$: half-life; VAP: ventilator-associated pneumonia.

CEFTOLOZANE TAZOBACTAM



Adequate cefiderocol concentrations were observed in the cerebrospinal fluid of one patient with meningitis

- **TDM** was performed in a patient with **meningitis** with **moderate renal impairment** (CrCL: 44.8 mL/min) who received cefiderocol at 2 g q6h (3-h IV infusion)
  - This high dose of cefiderocol is recommended for patients with augmented renal clearance, not impaired renal function, but was used to optimise cefiderocol penetration into the CSF

- Serum concentrations of **105 mg/L (C_{min})** and **170 mg/L (C_{max})** were observed

- CSF levels (13 mg/L) were measured 25 minutes before cefiderocol administration, concomitantly with serum trough concentrations, accounting for a **C_{min} CSF/serum ratio of 12.4%**

CSF, cerebrospinal fluid; CrCL, creatinine clearance; IV, intravenous; MIC, minimum inhibitory concentration; qnh, every n hours; TDM, therapeutic drug monitoring

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

INFEZIONE VIE URINARIE NON COMPLICATE: PSEUDOMONAS DIFFICULT TO TREAT (DTR)

		1° scelta	2° scelta
AIFA		**AMIKACINA** 15 mg/kg/dose singola **GENTAMICINA** 5 mg/kg/dose singola	**COLISTINA** 9 UI di carico poi 4.5 ogni 12 h **CEFTOLOZANO/TAZOBACTAM** 1.5 g EV ogni 8 h **CEFTAZIDIME/AVIBACTAM** 2.5 g EV ogni 8 h **IMIPEN/CILAST/RELEBACTAM** 1.25 mg EV ogni 6 h **CEFIDEROCOL** 2 g ogni 8 h
ESCMID		Vecchi farmaci attivi in vitro	
IDSA		**CEFEPIME** 2 g ogni 8 h in almeno 3 h **PIP-TAZO / CEFTAZIDIME / AZTREONAM se MIC S** **CEFTOLOZANO/TAZOBACTAM** 1.5 g EV ogni 8 h **CEFTAZIDIME/AVIBACTAM** 2.5 g EV ogni 8 h **IMIPEN/CILAST/RELEBACTAM** 1.25 mg EV ogni 6 h **CEFIDEROCOL** 2 g ogni 8 h	**AMIKACINA** 15 mg/kg/dose singola **GENTAMICINA** 5 mg/kg/dose singola **COLISTINA** 9 UI di carico poi 4.5 ogni 12 h
	MBL	**CEFIDEROCOL** 2 g ogni 8 h	

INFEZIONE VIE URINARIE COMPLICATE: PSEUDOMONAS DIFFICULT TO TREAT (DTR)

	1° scelta	2° scelta
AIFA	**AMIKACINA*** 20 mg/kg prima dose **GENTAMICINA*** 7 mg/kg/dose prima dose **CEFTOLOZANO/TAZOBACTAM** 1.5 g EV ogni 8 h	**CEFTAZIDIME/AVIBACTAM** 2.5 g EV ogni 8 h **IMIPEN/CILAST/RELEBACTAM** 1.25 mg EV ogni 6 h **CEFIDEROCOL** 2 g ogni 8 h
SIMIT-SITA-GISA-AMCLI-SIM	**CEFTO/TAZOBACTAM** 1.5 g EV ogni 8 h ± **FOSFOMICINA EV** 12-18 g EV divisa ogni 8-12 h **CEFTAZIDIME/AVIBACTAM** 2.5 g EV ogni 8 h ± **FOSFOMICINA EV**	**IMIPEN/CILAST/RELEBACTAM** 1.25 mg EV ogni 6 h ± **FOSFOMICINA EV** **CEFIDEROCOL** 2 g ogni 8 h ± **FOSFOMICINA EV**
ESCMID	**CEFTO/TAZOBACTAM** 1.5 g EV ogni 8 h	
IDSA	**CEFEPIME** 2 g ogni 8 h in almeno 3 h **PIP-TAZO / CEFTAZIDIME / AZTREONAM se MIC S** **CEFTOLOZANO/TAZOBACTAM** 1.5 g EV ogni 8 h **CEFTAZIDIME/AVIBACTAM** 2.5 g EV ogni 8 h **IMIPEN/CILAST/RELEBACTAM** 1.25 mg EV ogni 6 h **CEFIDEROCOL** 2 g ogni 8 h	**AMIKACINA** 15 mg/kg/dose singola **GENTAMICINA** 5 mg/kg/dose singola **COLISTINA** 9 UI di carico poi 4.5 ogni 12 h

* Dose successiva da regolare in base a PK/PD

Changing Epidemiology of CRBSIs

Pathogen	Hospital Wards[c]		Hospital ICUs[a]		Hospital Oncology Units[a]		LTACHs[a]	
	No. (%) Pathogens	Rank	No. (%) Pathogens	Rank	No. (%) Pathogens	Rank	No. (%) Pathogens	Rank
Staphylococcus aureus	5,386 (15.5)	1	2,497 (9.1)	3	1,163 (7.2)	6	1,217 (11.2)	3
Coagulase-negative staphylococci	3,792 (10.9)	2	3,789 (13.8)	1	1,681 (10.4)	2	1,277 (11.8)	2
Selected *Klebsiella* spp	3,344 (9.6)	3	1,708 (6.2)	8	1,441 (8.9)	4	1,158 (10.7)	4
Enterococcus faecalis[d]	2,636 (7.6)	4	2,117 (7.7)	5	664 (4.1)	8	1,314 (12.1)	1
Candida albicans[d]	2,469 (7.1)	5	2,844 (10.4)	2	216 (1.3)	15	642 (5.9)	7
Escherichia coli	2,279 (6.6)	6	1,129 (4.1)	9	2,667 (16.5)	1	394 (3.6)	10
Other *Candida* spp[d,e,f]	1,876 (5.4)	7	2,186 (8.0)	4	559 (3.5)	9	739 (6.8)	5
Enterococcus faecium[d]	1,673 (4.8)	8	1,981 (7.2)	6	1,670 (10.3)	3	691 (6.4)	6
Candida glabrata[d]	1,460 (4.2)	9	1,836 (6.7)	7	249 (1.5)	12	489 (4.5)	9
Enterobacter spp	1,453 (4.2)	10	1,078 (3.9)	10	532 (3.3)	10	383 (3.5)	11
Pseudomonas aeruginosa	1,407 (4.0)	11	1,061 (3.9)	11	701 (4.3)	7	495 (4.6)	8
Serratia spp	678 (1.9)	12	588 (2.1)	12	100 (0.6)	18	256 (2.4)	13
Acinetobacter spp	660 (1.9)	13	392 (1.4)	14	66 (0.4)	22	245 (2.3)	14
Other *Enterococcus* spp[d,e]	577 (1.7)	14	545 (2.0)	13	339 (2.1)	11	257 (2.4)	12
Viridans group streptococci	430 (1.2)	15	223 (0.8)	19	1,386 (8.6)	5	33 (0.3)	22
Other	4,668 (13.4)		3,422 (12.5)		2,757 (17.0)		1,238 (11.4)	
Total	34,788 (100.0)		27,396 (100.0)		16,191 (100.0)		10,828 (100.0)	

- **Adult ICUs:**
Candida species(27%), *Enterococcus* spp (17%), Enterobacteriaceae (16%)

- **Pediatric ICUs:**
Enterobacteriaceae(25%) *Enterococcus* species (19%), *Staphylococcusaureus* (14%)

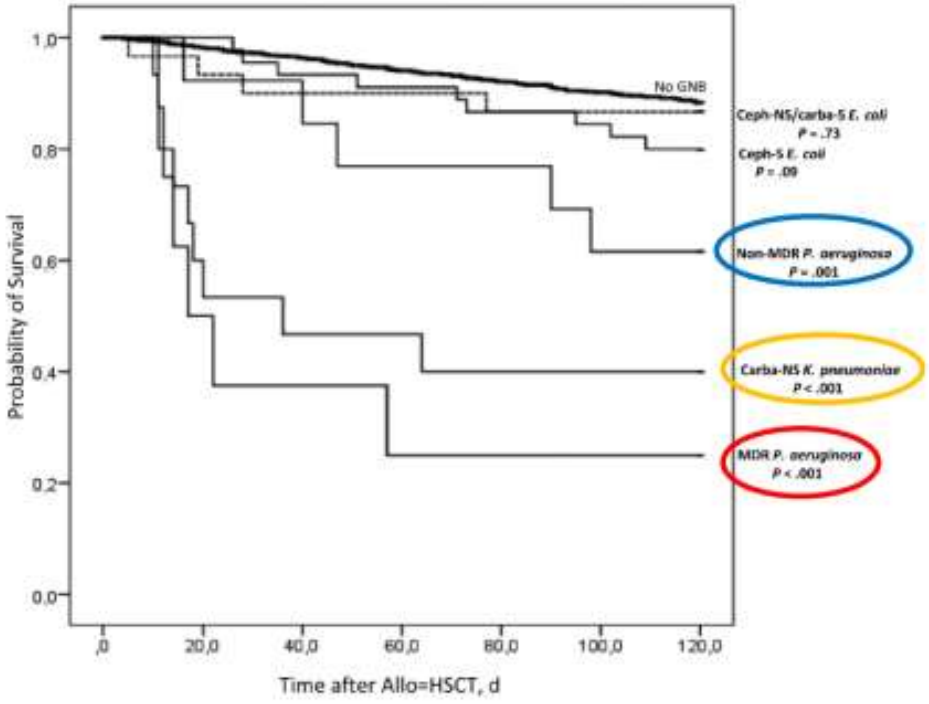
- **Adult wards:**
Enterobacteriaceae (23%), *S. aureus* (16%), *Enterococcus* species (13%)

- **Oncology wards:**
Enterobacteriaceae (31%) *Enterococcus* species (15%)

New analysis of data submitted to the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network (NHSN) from U.S. acute care hospitals **from 2011 through 2017** shows a notable change in the distribution of pathogens that cause these infections.

Timsit *et al. Ann. Intensive Care (2020) 10:118*
Novosad, S. et al. Infection Control & Hospital Epidemiology (2020),41(3), 313-319.

Probability of survival 4 months after allo-HSCT according to the development of pre-engraftment gram-negative BSI caused by different species.



Ginmenia C et al. Clin Infect Dis. 2017 Nov 13;65(11):1884-1896

PSEUDOMONAS DIFFICILE DA TRATTARE (DIFFICULT-TO-TREAT, DTR)

Terapia delle infezioni di cute e tessuti molli e delle infezioni in cui viene effettuato una buona bonifica del sito infettivo (ad esempio infezione addominale dopo un adeguato intervento chirugico di source control, batteriemie CVC-relate post rimozione del catetere) da Pseudomonas Difficile da Trattare (Difficult-to-Treat - DTR)

PSEUDOMONAS DTR		
INFEZIONI DI CUTE E TESSUTI MOLLI E INFEZIONI IN CUI VIENE EFFETTUATO UNA BUONA BONIFICA DEL SITO INFETTIVO		**Dosaggio**
Prima Scelta	**Ceftolozano-tazobactam**	1,5 g EV q8h
Seconda Scelta	**Ceftazidime-avibactam**	2,5 g EV q8h
	Imipenem-cilastatina-relebactam	1,25 g EV q6h
Alternative *se prima e seconda scelta non possibili*	**Cefiderocol**	2 g EV q8h
	Colistina	Dose da carico 9 mln UI EV seguita da 4,5 mln UI EV q12h

- ***Pseudomonas Difficile da Trattare (Difficult-to-Treat - DTR):*** ceppo resistente a ceftazidime, piperacillina-tazobactam, cefepime, aztreonam, meropenem, imipenem-cilastatina, levofloxacina, ciprofloxacina (definizione ESCMID, CMI 2022).
- EV: per via endovenosa.

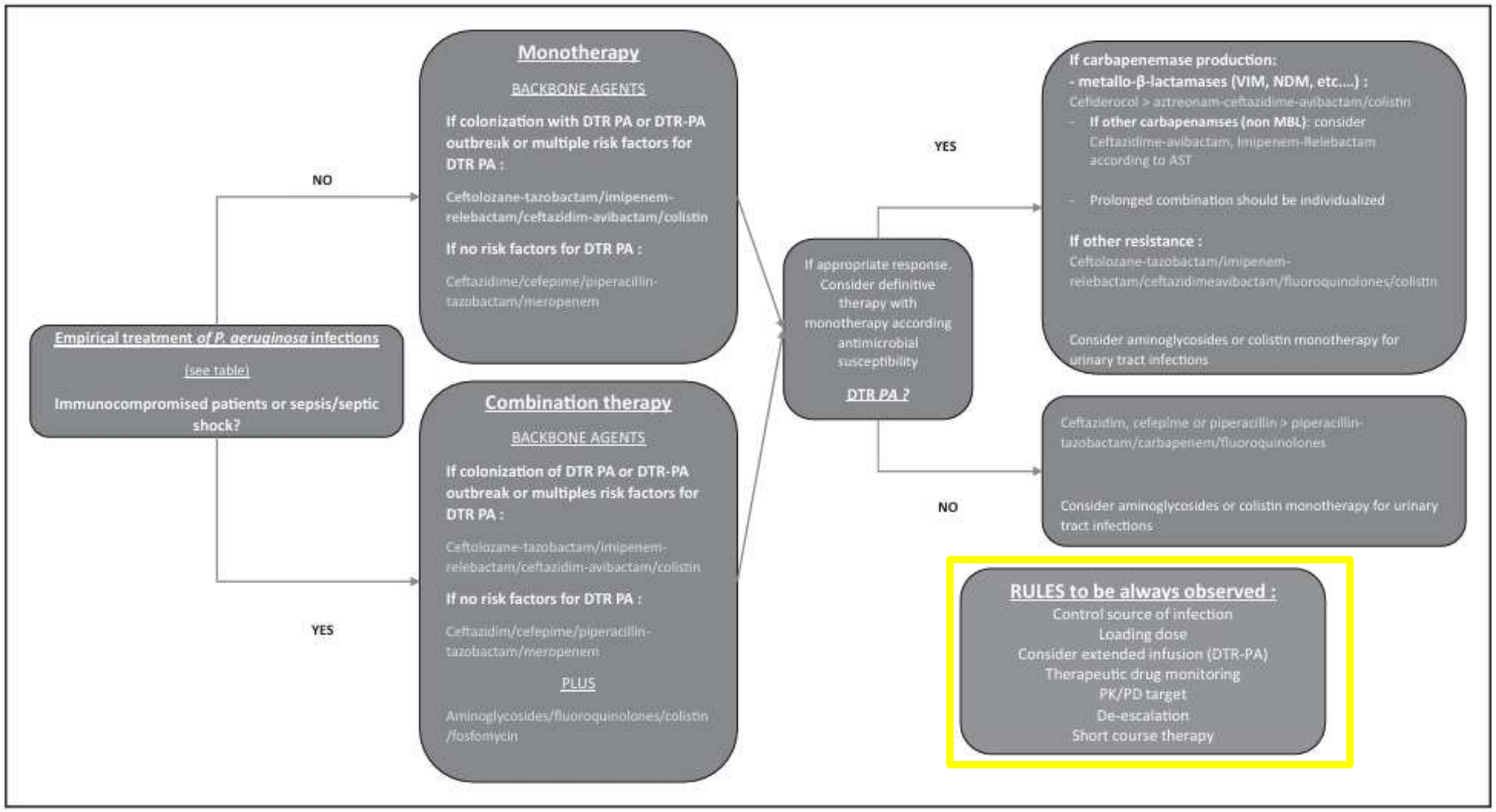


FIGURE 2. Empirical and adequate therapy for *P. aeruginosa* infections. DTR PA, difficult to treat *Pseudomonas aeruginosa*; MBL, metallo-β-lactamases; NDM, New-Delhi metallo-β-lactamases; PK/PD, pharmacokinetic/pharmacodynamic; VIM, Verona metallo-β-lactamases.

Terapia di combinazione:
sepsi
shock settico
ematologico neutropenico con BSI

Monoterapia mirata:
VAP (non vantaggi in outcome,
più eventi avversi)

Management strategies for severe Pseudomonas aeruginosa infections. Do Rego H, Timsit JF. Curr Opin Infect Dis. 2023 Dec 1;36(6):585-595.

FOSFOMICINA

Fosfomycin Synergistic activity

FOSFOMICINA E.V. IN COMBINAZIONE CON	PATOGENO
Piperacillina/Tazobactam	Escherichia coli/Klebsiella pneumoniae[3,4]
Ceftazidime/Avibactam	Klebsiella pneumoniae KPC[5]
	Pseudomonas aeruginosa MDR[6]
Ceftolozano/Tazobactam	Pseudomonas aeruginosa MDR[7]
Meropenem	Klebsiella pneumoniae KPC[8]
	Pseudomonas aeruginosa MDR[9]
	Escherichia coli ESBL[8]
Meropenem/Vaborbactam	Klebsiella pneumoniae KPC[17]
Colistina	Escherichia coli ESBL[8]
	Acinetobacter baumanni CR[10]
	Klebsiella pneumoniae KPC[11]
Daptomicina	Staphylococcus aureus - MRSA[12]
Rifampicina	Staphylococcus aureus - MRSA[13]
Linezolid	Staphylococcus aureus - MRSA[14]

- The mechanism of action of fosfomycin, affecting th involved in bacterial cell wall formation, suggests synergistic action in combination with other antibiotics.
- Intravenous fosfomycin has been administered in com other antibiotics for the treatment of nosocomial infe multidrug-resistant (MDR) Gram-positive and G bacteria.[2]
- Its unique mechanism of action may provide a synerg other classes of antibiotics including beta-lactams, am and fluoroquinolones.[2]

Source: 1. Gobernado M. Rev Esp Quimioterap 2003; 16 (1): 15-40. 2. Michalopoulos A. et al. Int J Infect Dis 2011; 15: e720-e726. 3. P presented at ASM microbe 2017. 4. Flavin R et al. Antimicrob Agents Chemother 2016; 60 (3): e605548-16. 5. Hong Nguyen M et al. ...id et al. The Journal of Infectious Diseases 2019; 220: 594-576. 7. Cuba G T et al. J Antimicrob Chemother 2020 Jul 1;75(7):1874-183 Microbiol Infect Dis 2012; 31: 595-76. 9. Orozano G L et al. Antimicrob Agents Chemother 2015; 62: e01652-18. 10. Leelaspipan S. et al. ... Zhao M. et al. J Antimicrob Chemother 2017; 72: 1895-1906. 12. Lee Y.G. et al. BMC Pharmacol Toxicol 2019; 20 (2): 13. Mihalcescu R. et a 2014; 58 (5): 2547-2553. 14. Chai D. et al. Biomed Res Int. 2015; 2015: 5413862. 15. Stamare A.C. et al. Antibiotics 2017; 6: 24. Cavalleri/Ichi del Postolo. 17. Oliva et al. Antibiotics (Basel). 2021 Jun 27;10(7):7

Indications & dosages

Indicazione	Dose giornaliera
Infezione complicata del tratto urinario	12–24 g[a] suddivisi in 2–3 dosi
Endocardite infettiva	12–24 g[a] suddivisi in 2–3 dosi
Infezioni ossee e articolari	12–24 g[a] suddivisi in 2–3 dosi
Polmonite contratta in ospedale, compresa la polmonite associata a ventilazione	12–24 g[a] suddivisi in 2–3 dosi
Infezioni complicate della cute e dei tessuti molli	12–24 g[a] suddivisi in 2–3 dosi
Meningite batterica	16–24 g[a] suddivisi in 3–4 dosi
Infezioni complicate intra-addominali	12–24 g[a] suddivisi in 2–3 dosi
Batteriemia che si verifica in associazione con, o si sospetta sia associata a, qualsiasi delle infezioni sopra elencate	12–24 g[a] suddivisi in 2–3 dosi

4 x 4g (16g) or 3 x 8g (24g) achieve appropriate PTA (90% according to EMA requirements) for bactericidal target in E.coli (clinical breakpoint for Enterobacterales = 32 mg/L)

Fosfomycin combined with Meropenem/vaborbactam and Cefiderocol

New italian recommendations on antibiotic therapy - II

Recommendation 6.2: In patients with invasive infections caused by **Pseudomonas aeruginosa** with difficult-to-treat resistance (DTR-PA), combination therapy should not be the routine choice but may be considered on a case-bycase basis, especially upon consultation with infectious diseases specialists. In particular, **combination regimens including fosfomycin as companion agent could be considered**

Table 2. Usual antimicrobial dosing in critically ill patients

Antibiotics	Antimicrobial dosing in normal hepatic and renal function
Amikacin	25–30 mg/kg/day single dose
Tobramycin	7–8 mg/kg/day single dose
Levofloxacin	500 mg every 12 h
Ciprofloxacin	400 mg every 8 h i.v. 750 mg every 12 h p.o.
Piperacillin-tazobactam	4.5 g loading dose 4.5 g every 6 h, infused over 4 h
Ceftazidime	2 g loading dose 2 g every 8 h, infused over 3 h
Cefepime	2 g loading dose 2 g every 8 h, infused over 3 h
Aztreonam	2 g loading dose 2 g every 6 h, infused over 3 h
Meropenem	2 g loading dose 2 g every 8 h, infused over 3 h
Imipenem-cilastin	1 g loading dose 1 g every 6 h, infused over 3 h
Ceftolozane-tazobactam	2 g/1 g; loading dose 2 g/1 g every 8 h, infused over 3 h
Ceftazidime-avibactam	2.5 g loading dose 2.5 g every 8 h, infused over 3 h
Imipenem-cilastin-relebactam	1 g loading dose 1 g every 6 h, infused over 3 h
Aztreonam + ceftazidime-avibactam	(2 g loading dose) and 2 g every 6 h, infused over 3 h + (2.5 g loading dose) and 2.5 g every 8 h, infused over 3 h (Caution: *both drugs should be administered simultaneously*)
Cefiderocol	2 g loading dose 2 g every 8 h, infused over 3 h
Colistin (CMS)	9 MUI (300 mg) loading dose 4.5 MUI (150 mg) every 12 h
Polymyxin B	20 000–25 000 UI/kg (2–2,5 mg/kg) loading dose 12 500–15 000 IU/kg (1.25–1.5 mg/kg) every 12 h
Fosfomycin	6–8 g every 8 h
Inhaled colistin	4 MUI every 8 h
Inhaled amikacin	400 mg every 8 h
Inhaled tobramycin	300 mg every 12 h

MUI, million units.

Clinical Microbiology and Infection 29 (2023) 165–1

Contents lists available at ScienceDirect

Clinical Microbiology and In

journal homepage: www.clinicalmicrobiologya

Narrative review

Observational versus randomized controlled trials to treatment durations: a narrative review

Emily G. McDonald [1, 2, 3, *], Connor Prosty [4], Ryan Hanula [3], Émilie Arthur M. Albuquerque [5], Steven Y.C. Tong [6, 7], Fergus Hamilton [8, 9]

[1] Division of General Internal Medicine, McGill University Health Centre, Montréal, Québec, Canada
[2] Clinical Practice Assessment Unit, Royal Victoria Hospital, McGill University Health Centre, Montréal, Québec, Ca
[3] Division of Experimental Medicine, Faculty of Medicine and Health Sciences, McGill University, Montréal, Québe
[4] Faculty of Medicine and Health Sciences, McGill University, Montréal, Québec, Canada
[5] School of Medicine, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil
[6] Victorian Infectious Diseases Service, The Royal Melbourne Hospital at the Peter Doherty Institute for Infection a
[7] Department of Infectious Diseases, The University of Melbourne at the Peter Doherty Institute for Infection and I
[8] MRC Integrative Epidemiology Unit, University of Bristol, Bristol, United Kingdom
[9] Infection Science, North Bristol NHS Trust, Bristol, United Kingdom
[10] Division of Infectious Diseases, McGill University Health Centre, Montréal, Québec, Canada

Table 1
Study characteristics

Author (y)	Bacteria	Short-course, (d), (interquartile range)	Short-course, (N)	Long-course, (d), (interquartile range)	Long-course, (N)	Notes
Randomized Controlled Trials						
Molina et al. [21] (2022)	Enterobacterales	Assigned to 7 d median: 7 (7–14)	110	Assigned to 14 d Median: 14 (14–16)	124	
von Dach et al. [2] (2020)	Mixed	Assigned to 7 d Median: 7 (range: 4–22)	169	Assigned to 14 d median: 14 (range: 5–17)	165	
Yahav et al. [22] (2019)	Mixed	Assigned to 7 d median: 7 (7–8)	306	Assigned to 14 d median: 14 (14–14)	298	
Retrospective cohort						
Bae et al. [14] (2021)	Pseudomonas	Cut-off range: 7–11 median: 9 (8–11)	97	Cut-off range: 12–21 median: 15 (14–18)	193	
Chotiprasitsakul et al. [20] (2018)	Enterobacterales	Cut-off range: 6–10 median: 9 (8–11)	385	Cut-off range: 11–16 median: 15 (13–15)	385	Propensity score–matched cohorts
Fabre et al. [19] (2019)	Pseudomonas	Cut-off range: 7–11 median: 9 (8–10)	72	Cut-off: 12–21 median: 16 (14–17)	179	Propensity score–weighted cohorts
Giannella et al. [18] (2018)	*Escherichia coli*	Cut-off: ≤10 median: 8 (6–9)	426	Cut-off: >10 median: 15 (12–20)	430	
Ruiz-Ruigómez et al. [17] (2021)	Mixed	Cut-off: ≤7 median: N/A	23	Cut-off: >7 median: NR	29	Only includes catheter-related bacteraemia.
Surapat et al. [16] (2020)	Mixed	Retrospective cases: Cut-off: ≤13 median: 10 (range: 7–13) Prospective Cases: Assigned to 7 (Range: 7–7)	41	Cut-off: >13 median: 17 (range, 14–39)	110	Only includes catheter-related bacteraemia. Data also include prospectively recruited cases assigned to 7 d of treatment.
Prospective cohort						
Sousa et al. [15] (2019)	Mixed	Cut-off range: 7–10 Median: 10 (7–9)	163	Cut-off: >10 Median: 14 (11–18)	232	

N/A Not applicable.

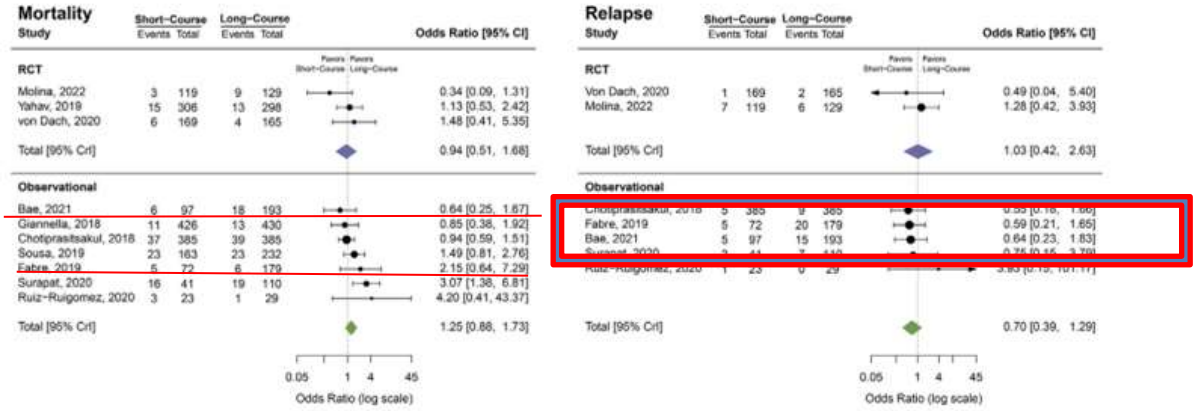


Fig. 2. Bayesian meta-analyses of (a) mortality and (b) relapse at 30 days stratified by randomized controlled trial versus observational study. RCT, randomized controlled trial.

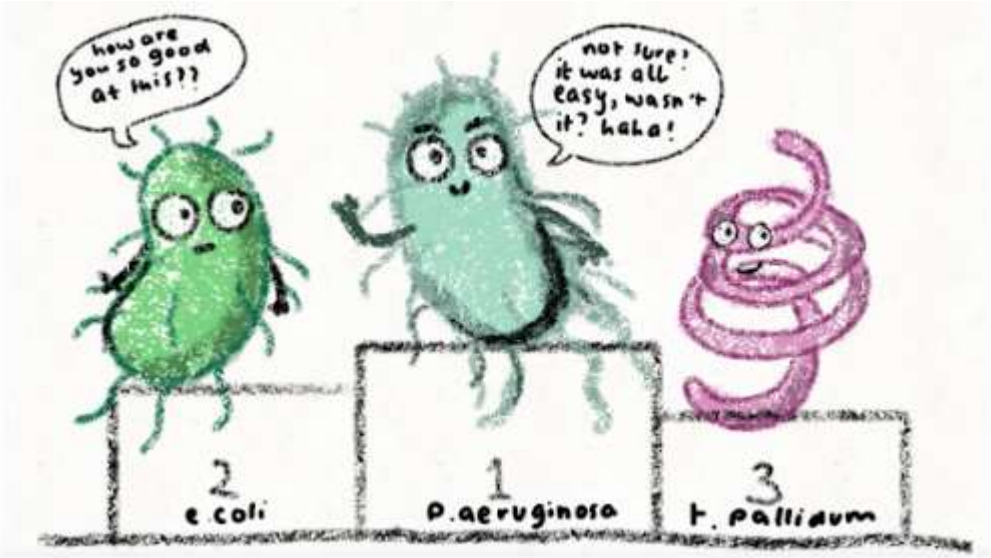
PA bacteremia a short course of treatment (6–10days) was showed as no different compared to a longer course (11–16days)

HAP/VAP 8 days vs 15: discordant results

Conclusioni

- *P. aeruginosa* è uno dei patogeni più comuni nel paziente critico.
- Asl città di Torino 7% circa di CRPA, segnalazione recente di VIM.
- Globalmente aumentano le resistenze in particolare MBL.
- Selezionare opportunamente il paziente con FR per CRPA (nota colonizzazione, outbreak nell'unità, esposizione prolungata a FQ/carbapenemi)
- Evitare overtreatment con carbapenemi in pazienti con PA wild type
- Importanza in particolare con i nuovi farmaci del source control per ridurre i tempi di terapia

Grazie per l'attenzione!



Nella pratica …

Uomo 86 anni.
APR: ipertensione, flutter in NAO, prostatectomia.
APP: 14/5 in DEA per vomito.
ECT addome colecisti distesa con grossolani calcoli.
EE rialzo colestasi e indici di flogosi (PCR 25 v.n. 0.5)

Visita chirurgica 1: avviare Tazocin 4.5 ogni 8 ore. Sospendere NAO.
Visita chirurgica 2: miglioramento clinico. Illustrati rischi e benefici , prosegue terapia antibiotica

Decorso complicato: trombosi portale, ematoma muscolo retto

Ecoendoscopia biliopancreatica: colecisti flogosata ispessita litiasica non calcoli nel coledoco

7/6 febbre, sopore e ipotensione. Eseguite emocolture escalation a meropenem
10/6 *P. aeruginosa* in corso antibiogramma

Microbiologia e Batteriologia

Materiale: Sangue da p.venoso periferico

Esame colturale in aerobiosi 1° set — *Esame in corso*

Isolato Pseudomonas aeruginosa ceppo produttore di carbapenemasi. Vitek conferma genotipica per batteri carbapenemasi produttori

1 Pseudomonas aeruginosa

Ceppo produttore di carbapenemasi

Ceppo 1 Pseudomonas aeruginosa

Antibiotici		MIC	MIC Breakpoint S<=	R>	Note
Aztreonam	I	16	0.001	16	
Cefepime	R	16	0.001	8	
Ceftazidima	R	32	0.001	8	
Ciprofloxacina	R	>2	0.001	0.5	
Colistina	R	>4	4	4	
Imipenem	R	>8	0.001	4	
Imipenem/Relebactam	R	>8	2	2	
Meropenem	R	>8	2	8	
Piperacillina/tazobactam	R	>64	0.001	16	
Tobramicina	R	>8	2	2	
Ceftolozane/Tazobactam	R	>16			
Ceftazidime/Avibactam	R	>8			

SISTEMA INTERPRETATIVO EUCAST

S = In Corso; I = Ceppo Sensibile R = Ceppo Resistente I = Ceppo intermedio (R= Insufficiente Evidenza

S*/R* = Categoria interpretativa presunta non supportata da Evidenza Clinica

S*/R* = Non è possibile erogare con antibiotici Beta Lattamici S*/I-R* = E' possibile erogare con antibiotici Beta Lattamici

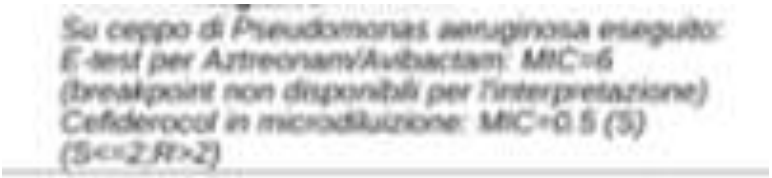
MIC = Minima Concentrazione Inibente in mg/ml ESBL = Ceppo produttore di Beta-Lattamasi a Spettro Allargato

Esame colturale in anaerobiosi 1° set	**Negativo**
Esame colturale in anaerobiosi 1° Set	**Negativo**

Nota: Si invia ceppo di Pseudomonas aeruginosa isolato da emocoltura per conferma carbapenemasi

Richiesta: **84288032** del **06/06/2025** Ore: 11:45

Esame	Esito	U.M.	Intervalli Riferimento	Metodica
Microbiologia e Batteriologia				
Materiale: Sangue da p.venoso periferico				
Enterobatteri. Test molecolare per carbapenemasi				
KPC	**Negativo**			Real time PCR
OXA-48	**Negativo**			Real time PCR
VIM	**Positivo**			Real time PCR
IMP	**Negativo**			Real time PCR
NDM	**Negativo**			Real time PCR



Su ceppo di Pseudomonas aeruginosa eseguito:
E-test per Aztreonam/Avibactam: MIC=6 (breakpoint non disponibili per l'interpretazione)
Cefiderocol in microdiluizione: MIC=0.5 (S) (S<=2 R>2)

Consulenza infettivologica 13/6:

stop meropenem avvia cefiderocol + tigeciclina

RM addome (16/6): colecisti distesa, pareti marcatamente ispessite, area ascessuale in stretta adiacenza con parenchima epatico a livello di S6. Trombosi portale nota. S3 formazione di possibile natura ascessuale.

17/6 trasferimento % Chirurgia Ospedale Giovanni Bosco per competenza

18/6 richiesta di consulenza infettivologica…

Grazie per l'attenzione!