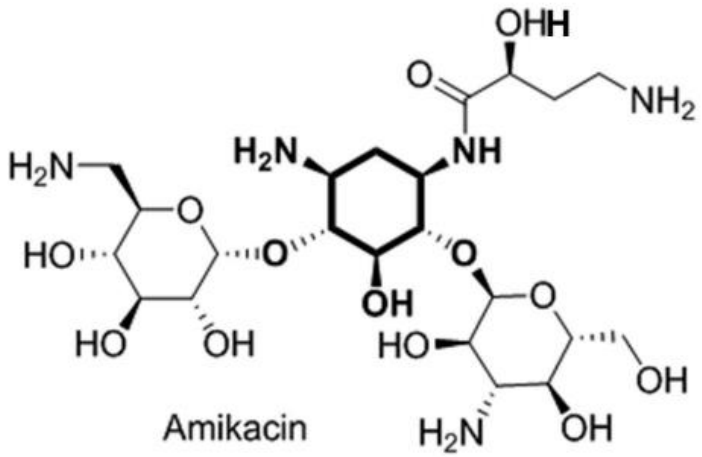
ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

ΠΜΣ
"ΛΟΙΜΩΞΙΟΛΟΓΙΑ"
ΤΗΣ ΙΑΤΡΙΚΗΣ ΣΧΟΛΗΣ
ΑΘΗΝΩΝ

Αμινογλυκοσίδες-Κεφταρολίνη

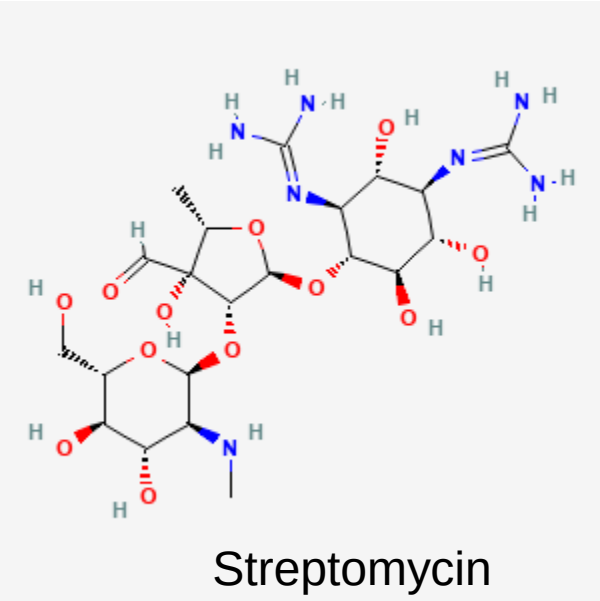


Amikacin

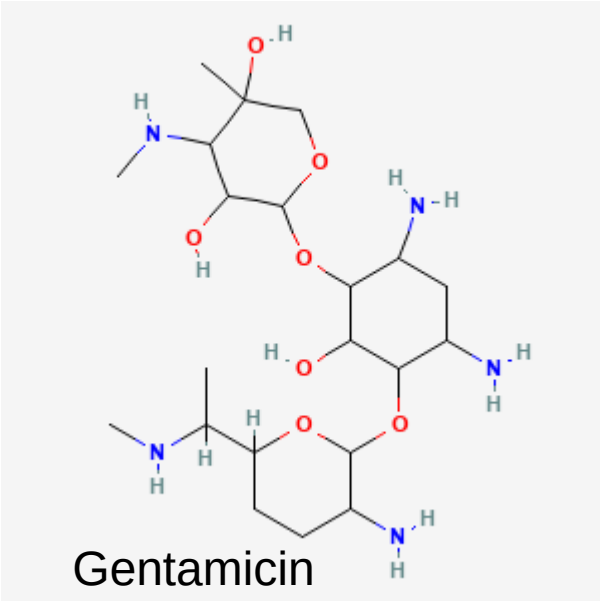
Ελένη Καρακικέ, MD, PhD
Παθολόγος-Λοιμωξιολόγος
Β΄Κλινική Εντατικής Θεραπείας, ΕΚΠΑ

Aminoglycosides

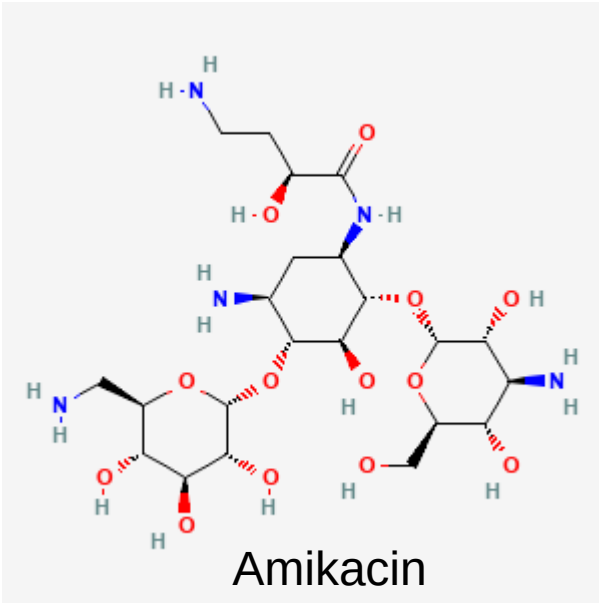
- Group of antimicrobials containing an aminocyclitol ring, to which amino sugars are attached by glycosidic linkages.
- Derived from actinomycetes
- In clinical practice since 1943



Streptomycin



Gentamicin

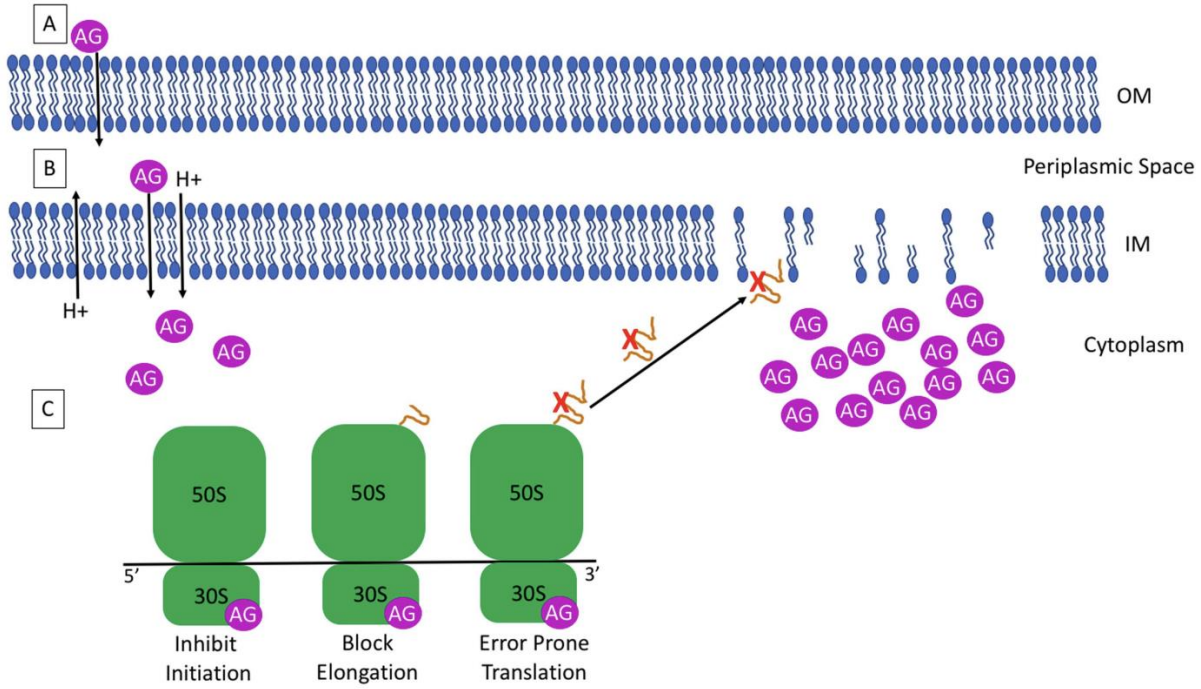


Amikacin

Germovsek E, et al. Arch Dis Child Educ Pract Ed. 2017;102(2):89-93.
https://pubchem.ncbi.nlm.nih.gov/

Μηχανισμός δράσης

- Binding to (-) charged components of the OM → diffusion to periplasmic space
- Energy-dependend crossing of the IM using proton motive force (aerobic conditions)
- bind to the decoding A-site of the 16S rRNA of the 30S ribosomal subunit of bacteria, resulting in the interference of protein synthesis → cell death
- and to helix 69 in the 50S ribosomal subunit hampering mRNA/tRNA translocation and ribosome recycling



Bellucci MC,et al. 2020 Aug 11;9(8):504.
Serio AW, et al. EcoSal Plus. 2018 Nov;8(1).

Antimicrobial Spectrum		
Gram (-) bacteria		
	Enterobacteriaceae	Including MDR
	P. aeruginosa	
	A. baumannii	To a lesser degree
	Y. pestis	
	F. tularensis	
Gram (+) cocci		**Not as monotherapy!**
	Staphylococcus spp	Including MRSA, VISA, VRSA
	Enterococcus spp	Synergistic if low level-resistance
Mycobacteria spp		
	M. tuberculosis	Second line treatment
	M. avium complex	
Anaerobic bacteria		**NO activity**
Parasites		
	E. histolytica	

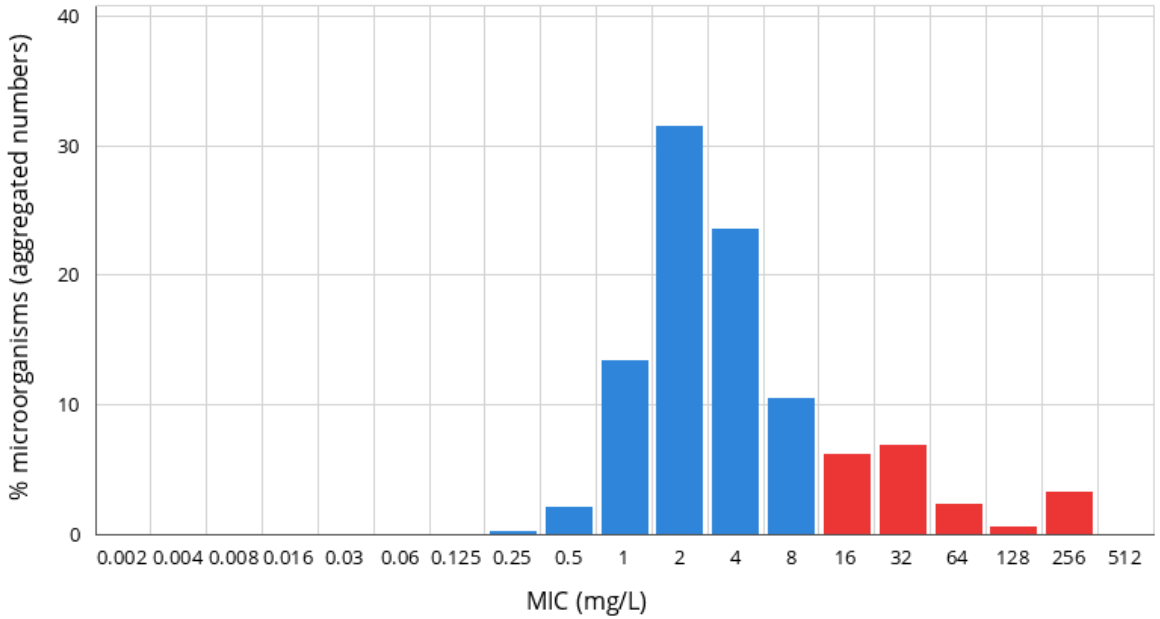
Krause KM, et al. Cold Spring Harb Perspect Med. 2016;6(6):a027029.

MICs and ECOFFs for amikacin

A. baumannii

Amikacin / Acinetobacter baumannii
International MIC distribution - Reference database 2023-11-03
Based on aggregated distributions

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



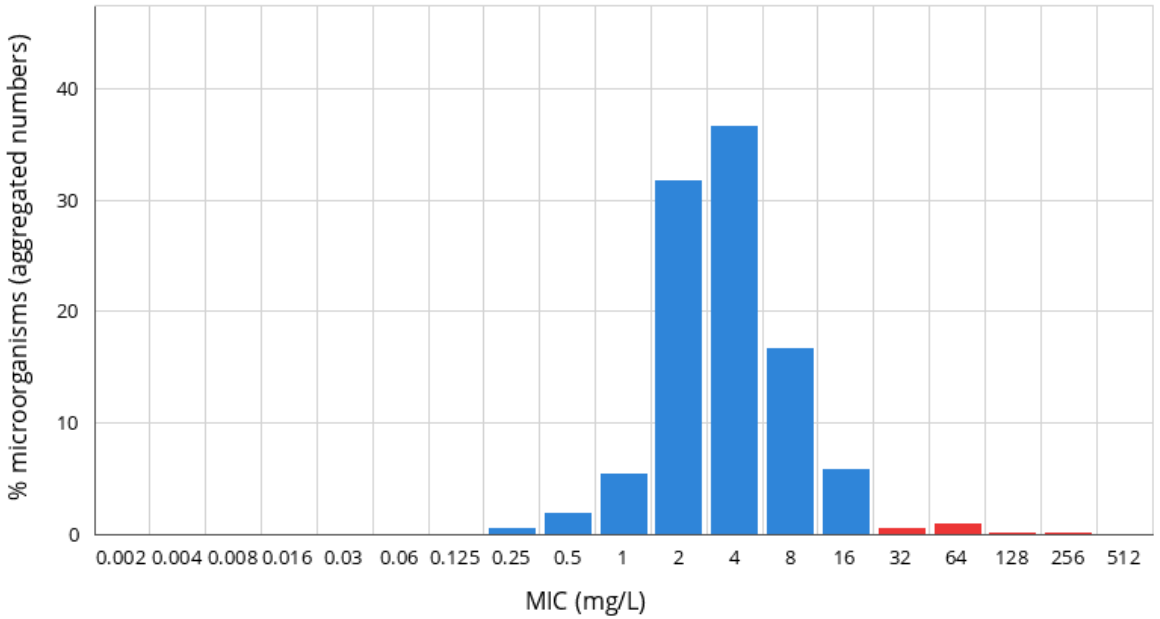
MIC
Epidemiological cut-off (ECOFF): 8 mg/L
Wildtype (WT) organisms: ≤ 8 mg/L

Confidence interval: 2 - 16
2194 observations (8 data sources)

P. aeruginosa

Amikacin / Pseudomonas aeruginosa
International MIC distribution - Reference database 2023-11-03
Based on aggregated distributions

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance



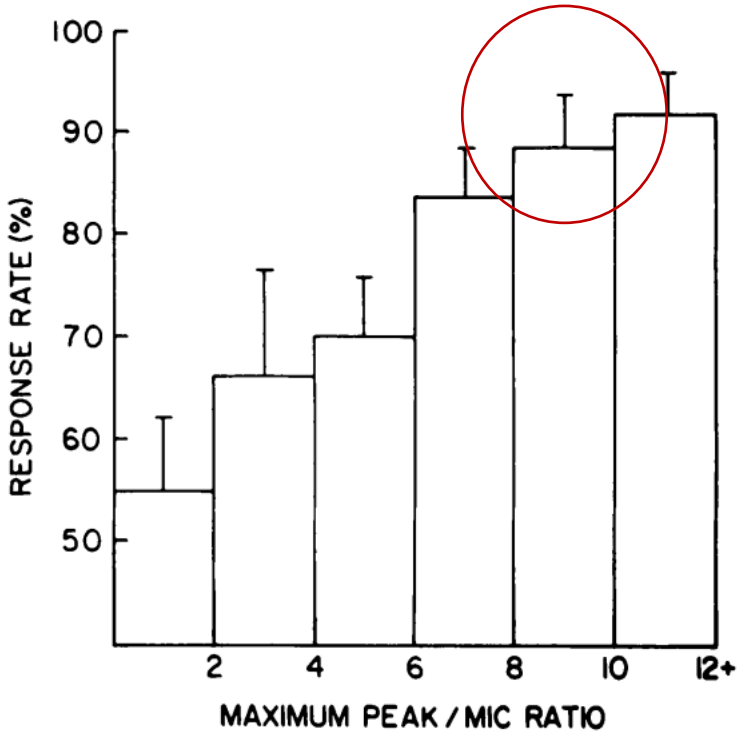
MIC
Epidemiological cut-off (ECOFF): 16 mg/L
Wildtype (WT) organisms: ≤ 16 mg/L

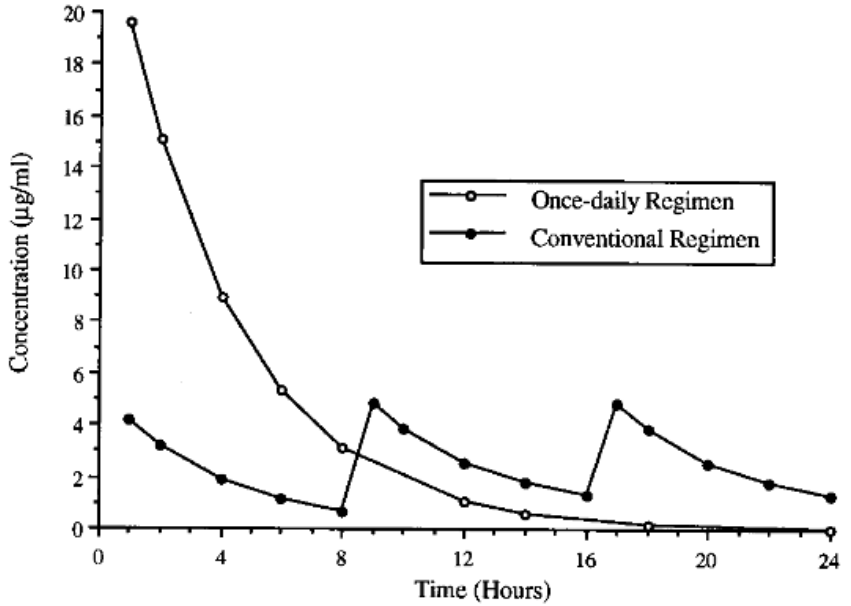
Confidence interval: 4 - 32
17029 observations (12 data sources)

https://www.eucast.org/clinical_breakpoints

PK/PD profile

- Parameters for efficacy
  - C_{max}/ MIC: 8-10
  - AUC/MIC ≥ 70 and ≤ 120
- Dosing
  - Amikacin (15-) 25-30 (-35) mg/kg (TBW) /day → C_{max} >60 mg/l
  - Gentamicin (5-) 7-7.5 mg/kg (TBW)/day → C_{max} >30 mg/l
- Single over multiple daily dosing
- Hydrophilic
  - Difficult penetration in several compartments (ELF, CSF, bone, abcess)→ interest of direct infected-site delivery?
  - Exclusive renal clearance





Moore RD, et al. J Infect Dis. 1987;155(1):93-9.
Germovsek E, et al. Arch Dis Child Educ Pract Ed. 2017;102(2):89-93
https://www.eucast.org/publications-and-documents/rd
Nicolau DP, et al. Antimicrob Agents Chemother. 1995;39(3):650-5.

Arguments for single-day dosing

Cochrane Database of Systematic Reviews | Review - Intervention

Once-daily versus multiple-daily dosing with intravenous aminoglycosides for cystic fibrosis

Jayesh Bhatt, Nikki Jahnke, Alan R Smyth Authors' declarations of interest

Version published: 04 September 2019 Version history

https://doi.org/10.1002/14651858.CD002009.pub7

JOURNAL ARTICLE

Once versus multiple daily dosing of aminoglycosides for patients with febrile neutropenia: a systematic review and meta-analysis

FREE

Michael N. Mavros, Konstantinos A. Polyzos, Petros I. Rafailidis, Matthew E. Falagas

Journal of Antimicrobial Chemotherapy, Volume 66, Issue 2, February 2011, Pages 251–259, https://doi.org/10.1093/jac/dkq451

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Mar. 1995, p. 650–655
0066-4804/95/$04.00+0
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Vol. 39, No. 3

Experience with a Once-Daily Aminoglycoside Program Administered to 2,184 Adult Patients

DAVID P. NICOLAU,[1,2,3]* COLLIN D. FREEMAN,[1,3]† PAUL P. BELLIVEAU,[1,3]‡ CHARLES H. NIGHTINGALE,[3,4] JACK W. ROSS,[2] AND RICHARD QUINTILIANI[2,5]

Once versus Twice Daily Gentamicin Dosing for Infective Endocarditis: A Randomized Clinical Trial

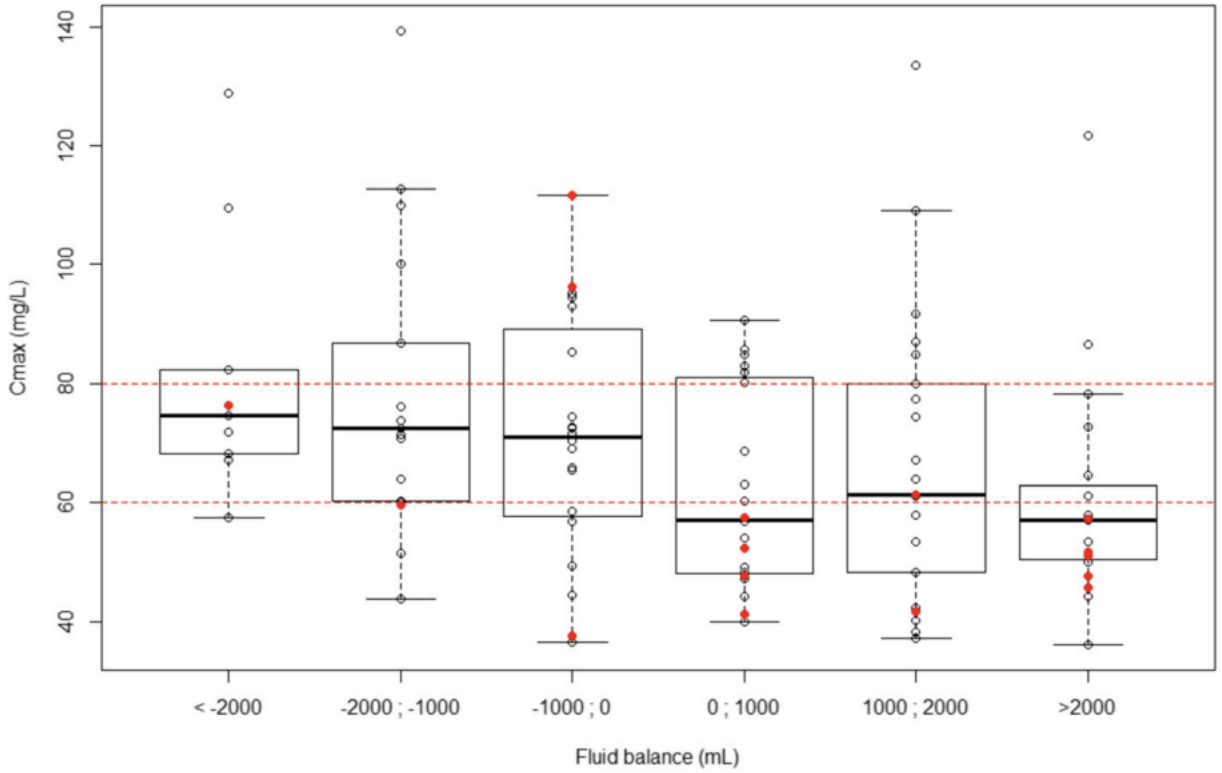
Subject Area: Cardiovascular System

Kristine Buchholtz; Carsten Toftager Larsen; Bente Schaadt; Christian Hassager; Niels Eske Bruun

Cardiology (2011) 119 (2): 65–71.
https://doi.org/10.1159/000329842 Article history

Is it enough for the critically ill (amikacin)?

- N=106 patients with ECMO
- Standard once daily 25 mg/kg dosing resulted in suboptimal C_{max} (<60 mg/l) in 39% of cases
- Lower BMI and a (+) 24h fluid balance were independent risk factors for under-dosing
- Suggestion of
  - 25 mg/kg if (-) fluid balance
  - 30-35 mg/kg if (+) fluid balance



Touchard C, et al. Crit Care. 2018;22(1):199.

Is it enough for the critically ill (gentamicin)?

- N=34 patients in the ICU
- Standard once-daily 8mg/kg dosing resulted in suboptimal C_{max} (<30 mg/l) in all cases
- (+) 24h fluid balance was the only independent risk factor for underdosing
- 29 vs 60% mortality in C_{max} >16 mg/l; p=0.09

Gentamicin pharmacokinetic/pharmacodynamic parameters.

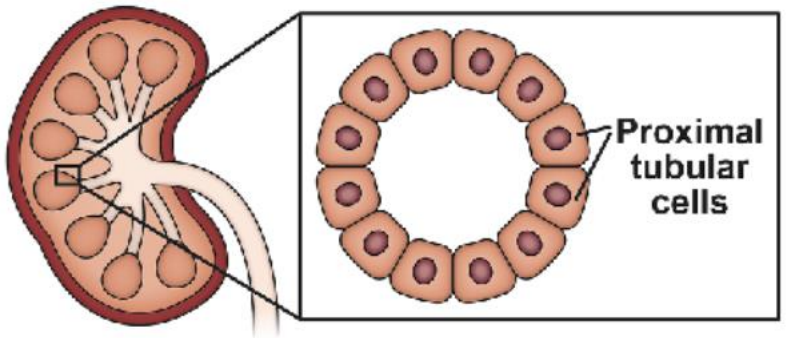
Variable	$n = 34$
Dose (mg)	560 [510–610]
Dose (mg/kg of total body weight of the day)	8 [7.9–8.1]
Peak concentration (mg/L)	17.5 [15.4–20.7]
Patients with peak concentration > 30 mg/L	0
Patients with peak concentration > 16 mg/L	24 (71)
Patients with peak concentration > 8 mg/L	33 (97)
Trough concentration	1.6 [0.7–3.3]

Results are expressed as medians [25th–75th percentiles] or *n* (%).

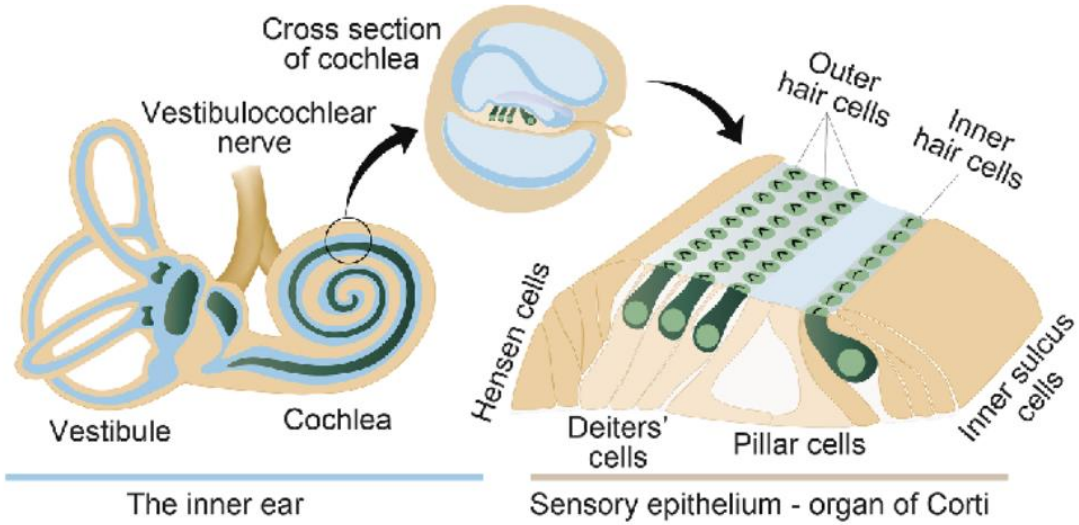
Allou N, et al. Anaesth Crit Care Pain Med. 2016;35(5):331-335.

Toxicity

Higher risk if >5 days treatment, higher cumulative dose and repeated dosing

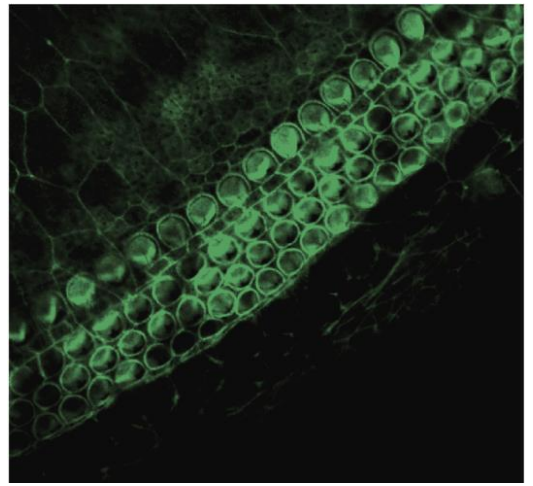


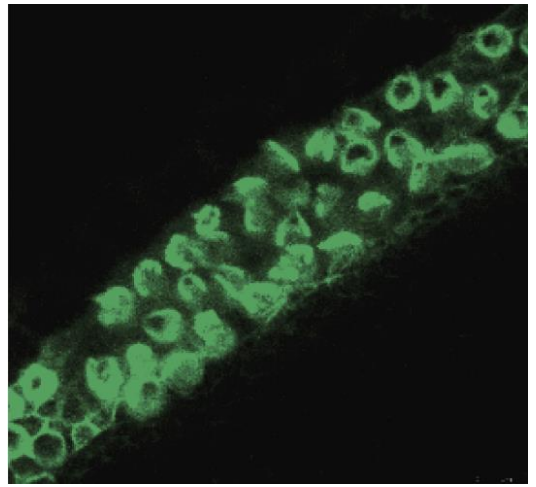
Acute kidney injury with preserved diuresis, tubular necrosis



Vertigo, ataxia, nystagmus

Tinittus, hearling loss→ mostly permanent





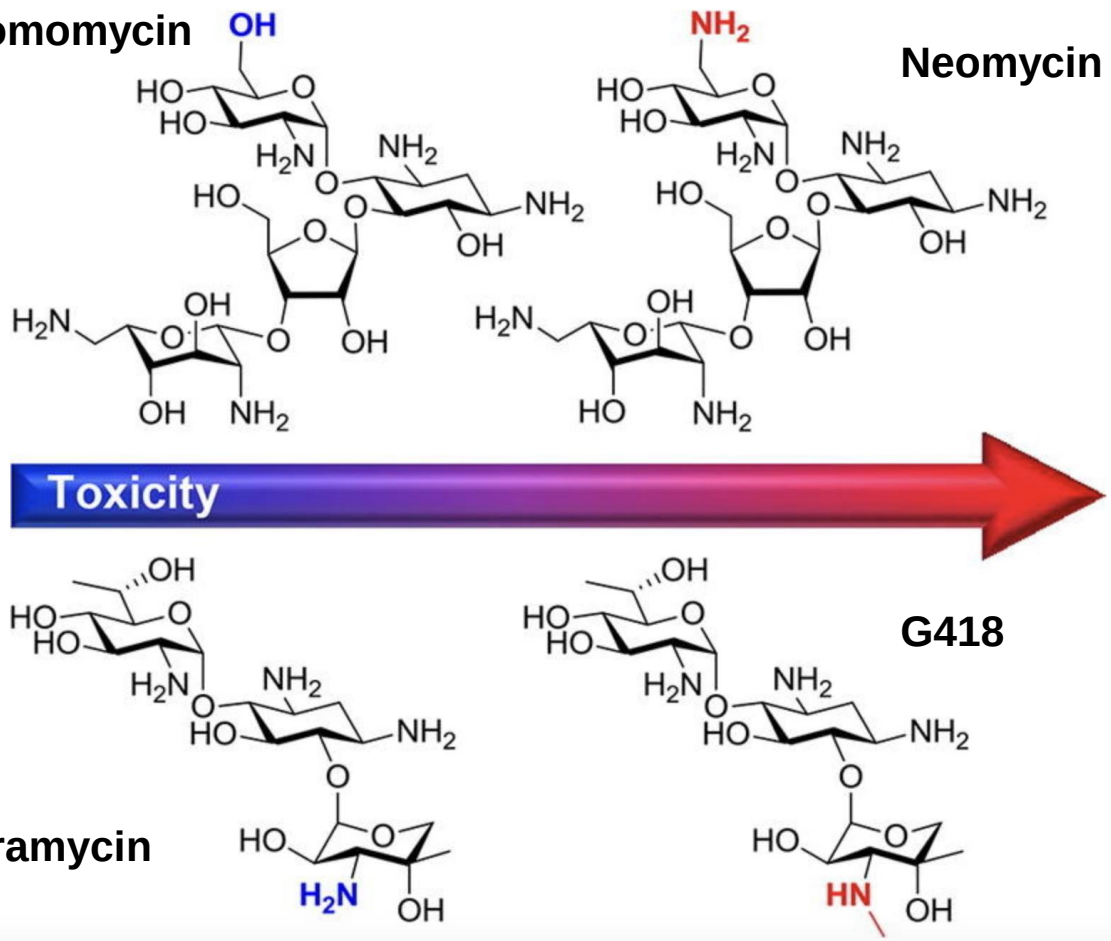
Neuromuscular blocade: reversible, anticholinesterase treatment. CI myasthenia gravis!!!

Jospe-Kaufman M, et al. Bioorg Med Chem Lett. 2020;30(13):127218
Thy M, et al. Antibiotics (Basel). 2023;12(5):860

Caution required

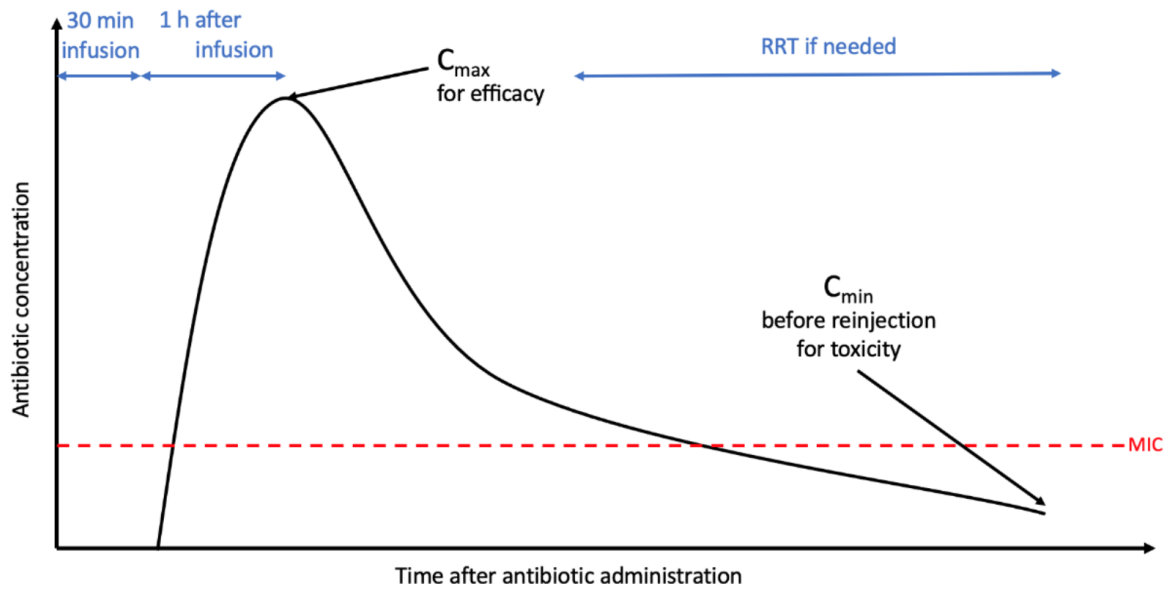
Paromomycin

Neomycin B



G418

Apramycin



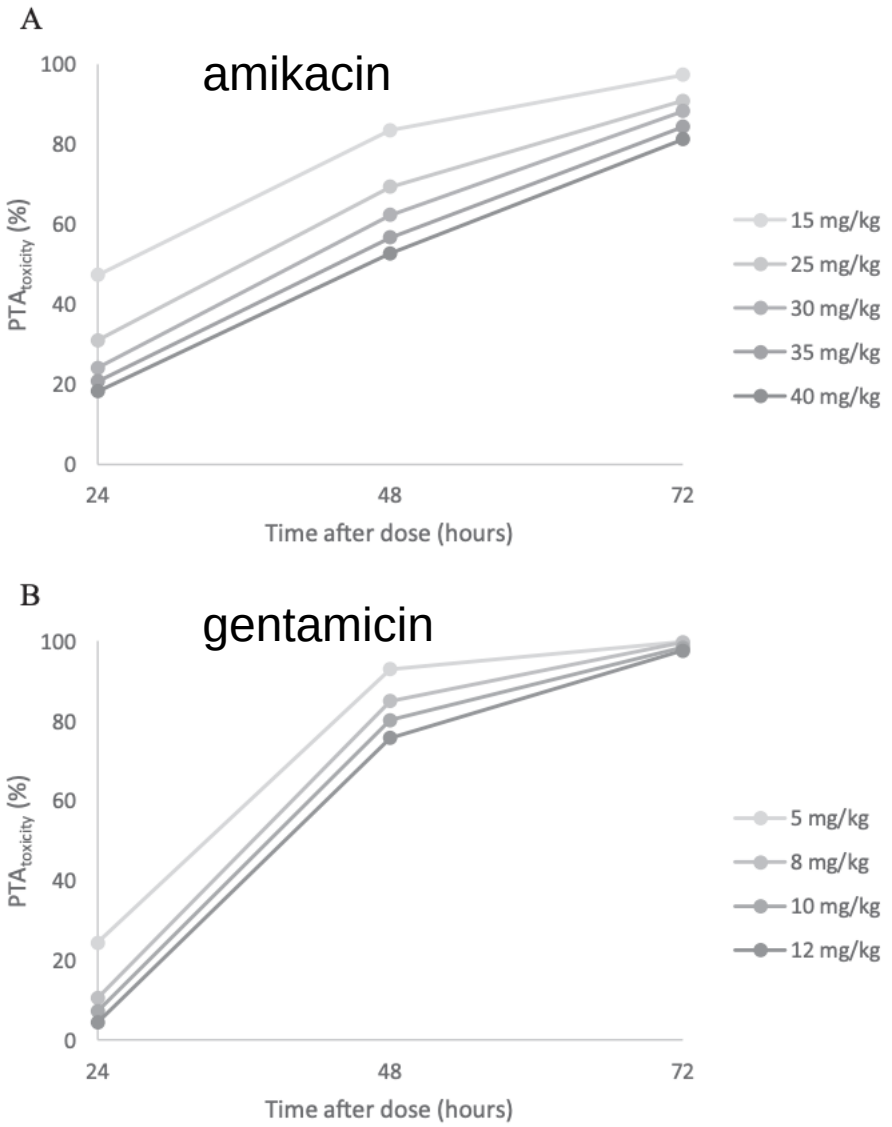
	C_{min} (trough) target threshold*
Amikacin	≤ 2.5 mg/l
Gentamicin	≤ 0.5 mg/l

Jospe-Kaufman M, et al. Bioorg Med Chem Lett. 2020;30(13):127218.
Duong A, et al. Antibiotics (Basel). 2021;10(5):507
Thy M, et al. Antibiotics (Basel). 2023;12(5):860

* Recommended if treatment expected to last >5 days

Thus (even in renal impairement)

- No change of the initial dose
- Adapt dosing intervals
- Probability of target attainment regarding toxicity (C_{min} <2.5 mg/l for amikacin and <0.5 mg/l for gentamicin) remains comparable at larger intervals
- Nephrotoxicity 1.2% vs historical 3-5% after a 7-day therapy

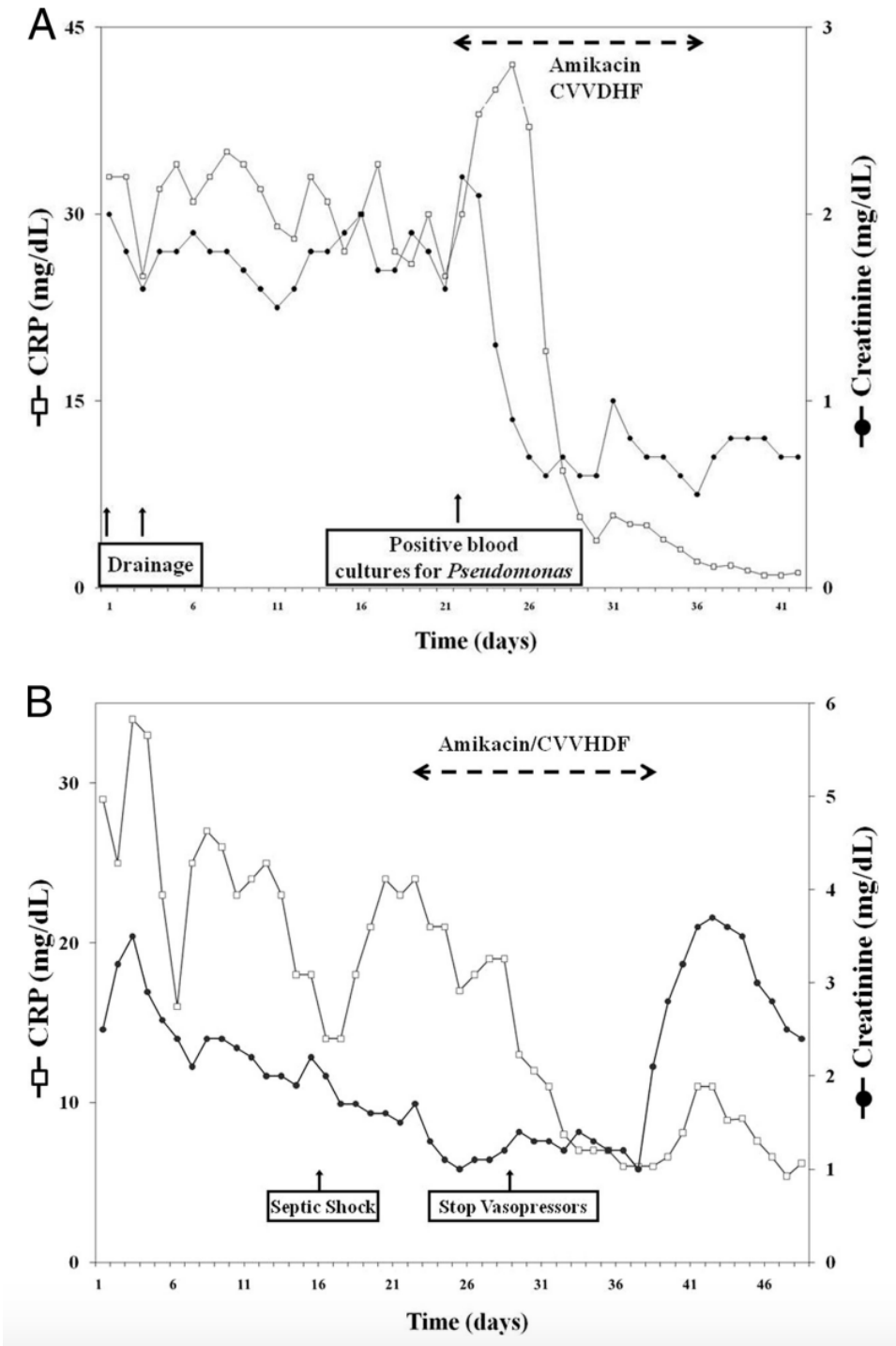


Marsot A, et al. Int J Antimicrob Agents. 2020;56(4):106124.
Nicolau DP, et al. Antimicrob Agents Chemother. 1995;39(3):650-5

What does this mean practically?

- N=2 patients with sepsis/ septic shock and XDR P. aeruginosa (VIM) infection
- Colistin-based combination treatment failure
- Amikacin I (MIC: 16)
- Amikacin 25 mg/kg (2500 mg)/day followed by CVVHDF 2h later
- TDM-based dosing of 30-50 mg/kg (3000-6000 mg)/day
- Normalization of inflammatory parameters
- Alive ICU discharge
- Serum creatinine values at discharge were similar to those before ICU admission

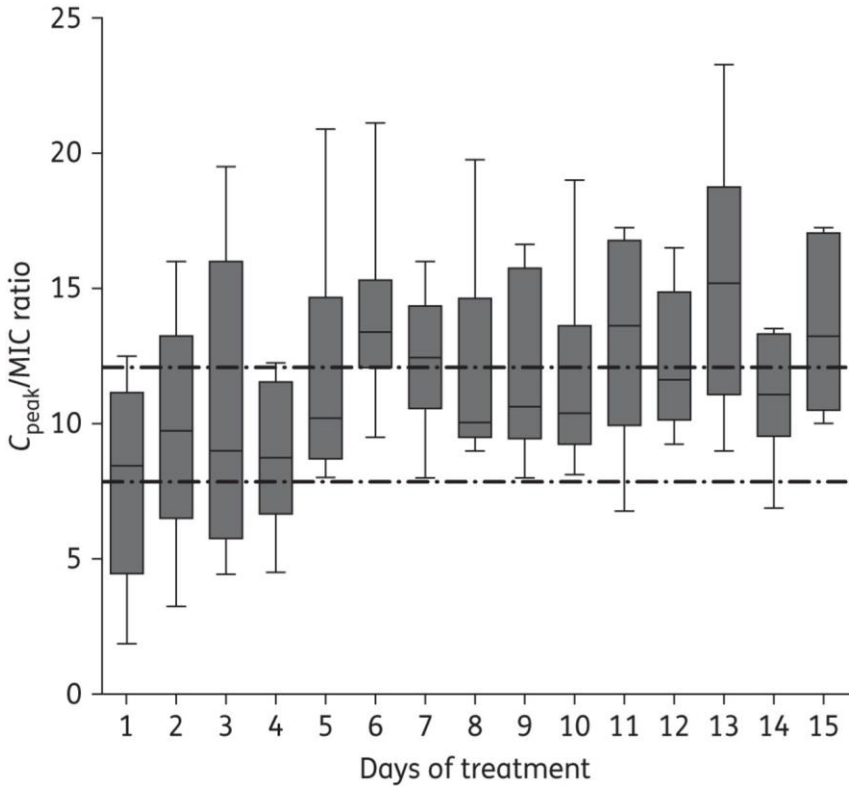
Layeux B, et al. Antimicrob Agents Chemother. 2010; 54(11):4939-41.



Proof of concept

- N=15 patients with sepsis/ septic shock due to DTR Gram (-)
- Failure of other options
- High dose aminoglycoside regimen, followed by CVVHDF and TDM-based adaptation
- 8 patients (53%) had clinical response

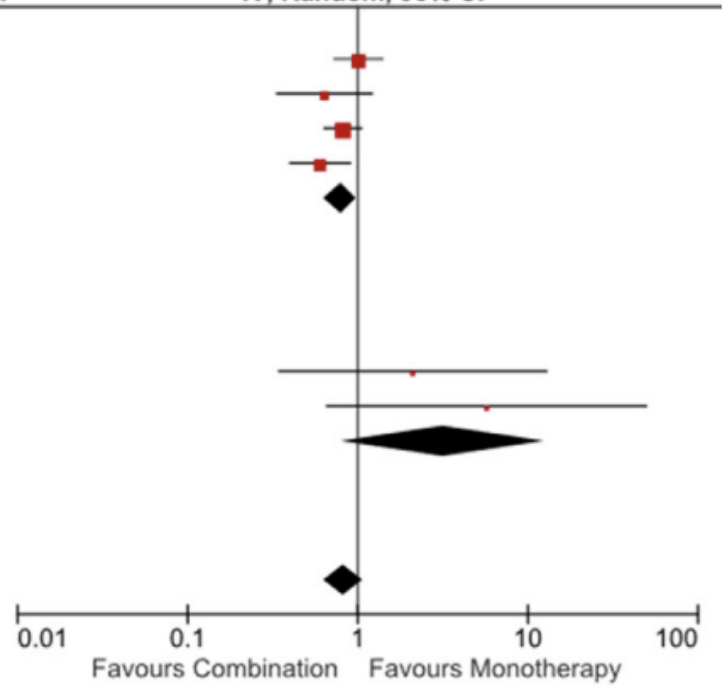
Drug	Initial dose (mg/kg)	Maximal daily dose (mg/kg)	Initial peak (mg/L)	Number of patients with optimal C_{peak}/MIC on day 1	Total dose (mg)
Amikacin (*n*=11)	29 (25–37)	29 (26–67)	77 (66–89)	8	22500 (14 250–37 875)
Gentamicin (*n*=3)	11 (10–18)	13 (11–18)	27 (21–39)	2	14400 (7900–16 800)
Tobramycin (*n*=1)	16	20	15	0	12480



Brasseur A, et al. J Antimicrob Chemother. 2016;71(5):1386-94.

Combination treatment in severe infections

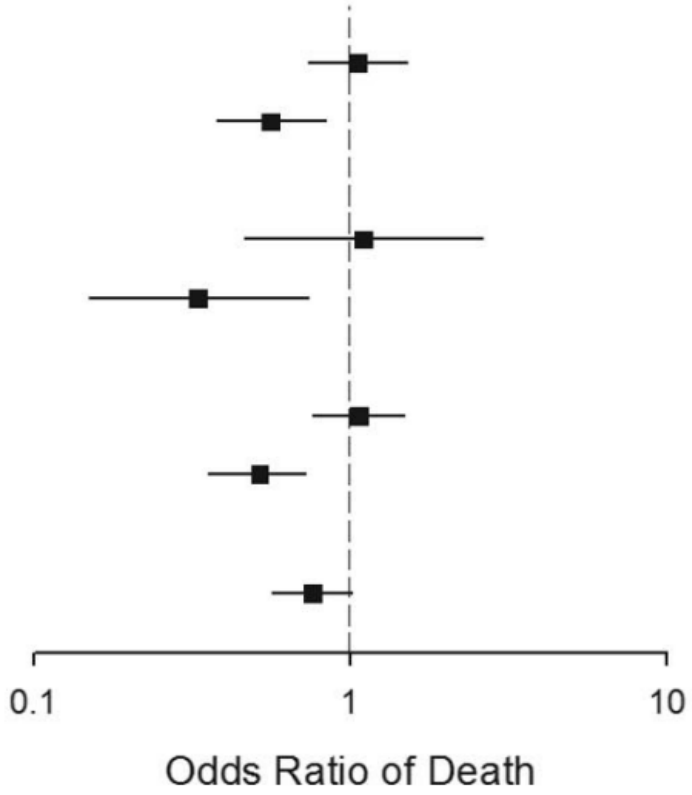
Study or Subgroup	log[Odds Ratio]	SE	Combination Therapy Total	Monotherapy Total	Weight	Odds Ratio IV, Random, 95% CI
1.5.1 Cohort Studies						
Freundlich, 2007	0.009496	0.165816	969	288	27.7%	1.01 [0.73, 1.40]
Garnacho-Montero, 2007	-0.45107	0.327542	68	63	12.7%	0.64 [0.34, 1.21]
Kumar, 2010	-0.20131	0.127108	359	930	33.3%	0.82 [0.64, 1.05]
Martinez, 2010	-0.51083	0.20687	168	664	22.6%	0.60 [0.40, 0.90]
Subtotal (95% CI)			**1564**	**1945**	**96.4%**	**0.79 [0.64, 0.99]**
Heterogeneity: Tau² = 0.02; Chi² = 4.41, df = 3 (P = 0.22); I² = 32%						
Test for overall effect: Z = 2.06 (P = 0.04)						
1.5.2 Randomized Controlled Trials						
Damas, 2006	0.74444	0.923381	19	20	2.1%	2.11 [0.34, 12.86]
Speich, 1998	1.744131	1.101959	43	41	1.5%	5.72 [0.66, 49.60]
Subtotal (95% CI)			**62**	**61**	**3.6%**	**3.18 [0.79, 12.73]**
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (*P* = 0.49); I² = 0%						
Test for overall effect: Z = 1.63 (*P* = 0.10)						
Total (95% CI)			**1626**	**2006**	**100.0%**	**0.82 [0.63, 1.08]**
Heterogeneity: Tau² = 0.04; Chi² = 8.60, df = 5 (*P* = 0.13); I² = 42%						
Test for overall effect: Z = 1.43 (*P* = 0.15)						
Test for subgroup differences: Chi² = 3.76, df = 1 (*P* = 0.05), I² = 73.4%						



Heffernan AJ, et al. Int J Antimicrob Agents. 2020;55(3):105839.

Combination treatment in the subgroup with septic shock

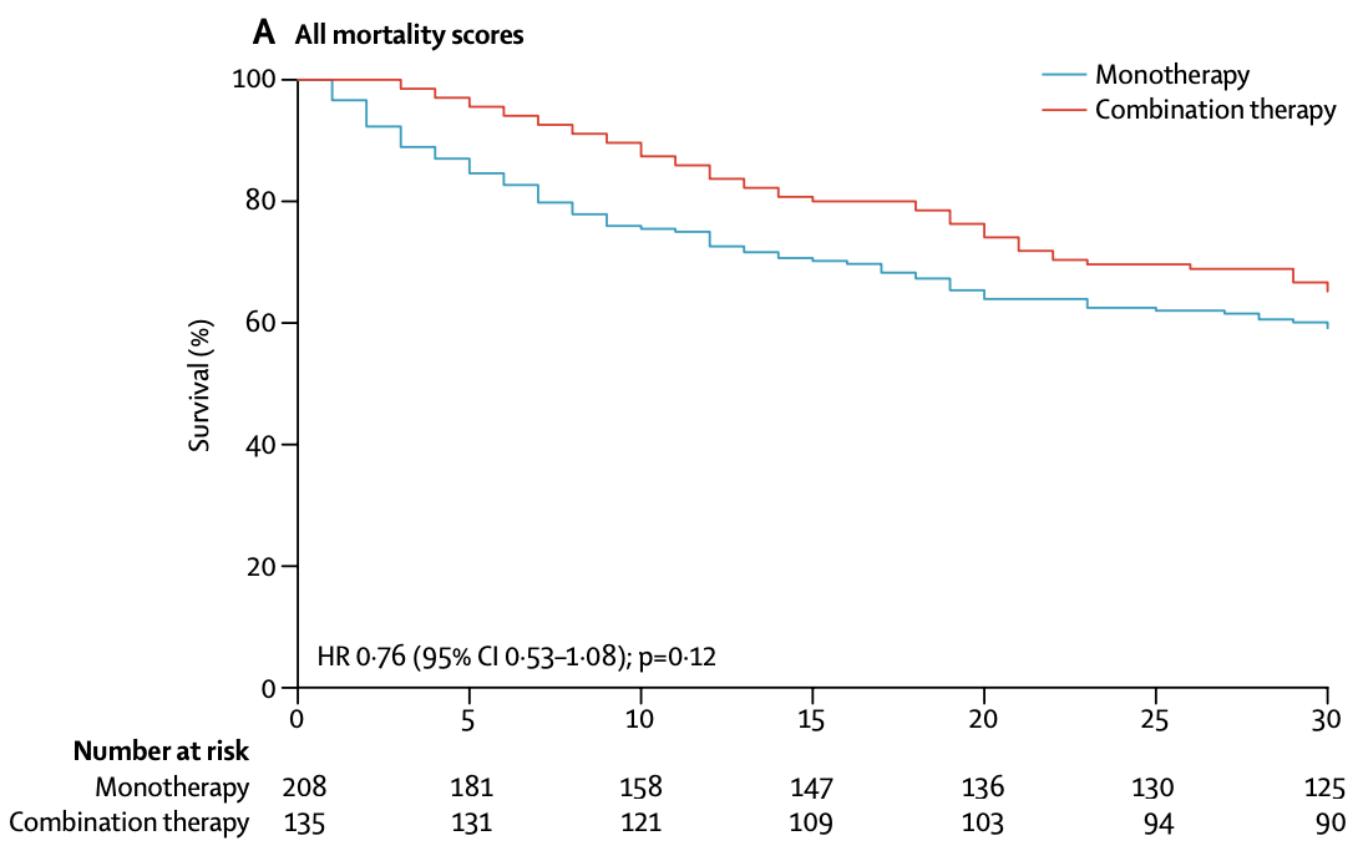
Group	Monotherapy Mortality (%)	Combination Therapy Mortality (%)	Odds Ratio	I^2 (%)	P-value
non-shock	86/680 (12.6)	96/666 (14.4)	1.06 (0.73-1.52)	13.7	.7721
shock	96/188 (51.1)	177/422 (41.9)	0.56 (0.39-0.83)	0.8	.0043
non-critically ill	23/313 (7.3)	35/339 (10.3)	1.10 (0.46-2.60)	45.3	.8321
critically ill	32/64 (50.0)	34/128 (26.6)	0.33 (0.15-0.74)	0	.0067
non-shock/non-critically ill	109/993 (11.0)	131/1005 (13.0)	1.06 (0.76-1.47)	19.1	.7178
shock/critically ill	128/252 (50.1)	211/550 (38.4)	0.51 (0.36-0.72)	0	.0002
overall	237/1245 (19.0)	342/1555 (22.0)	0.76 (0.57-1.02)	33.8	.0622

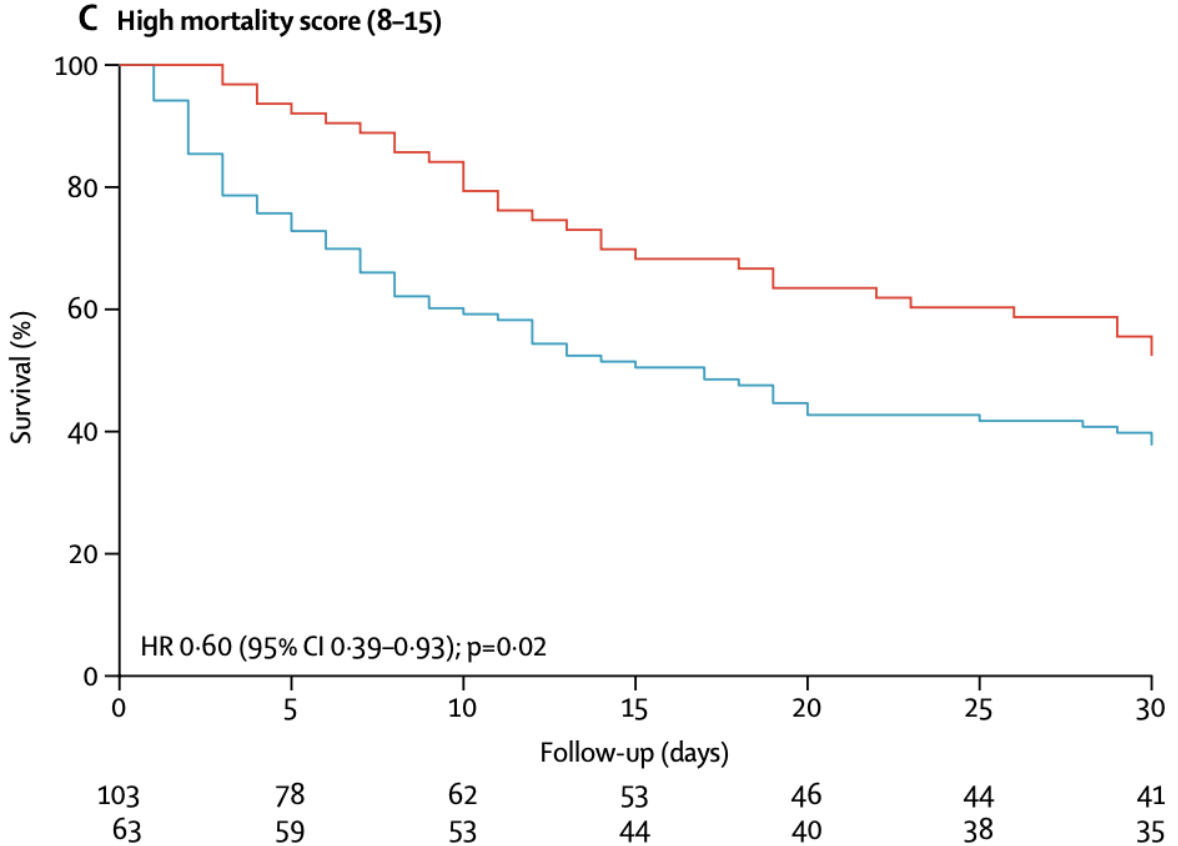


Kumar A, et al. Crit Care Med. 2010;38(8):1651-64.

Combination treatment in infections caused by CPE

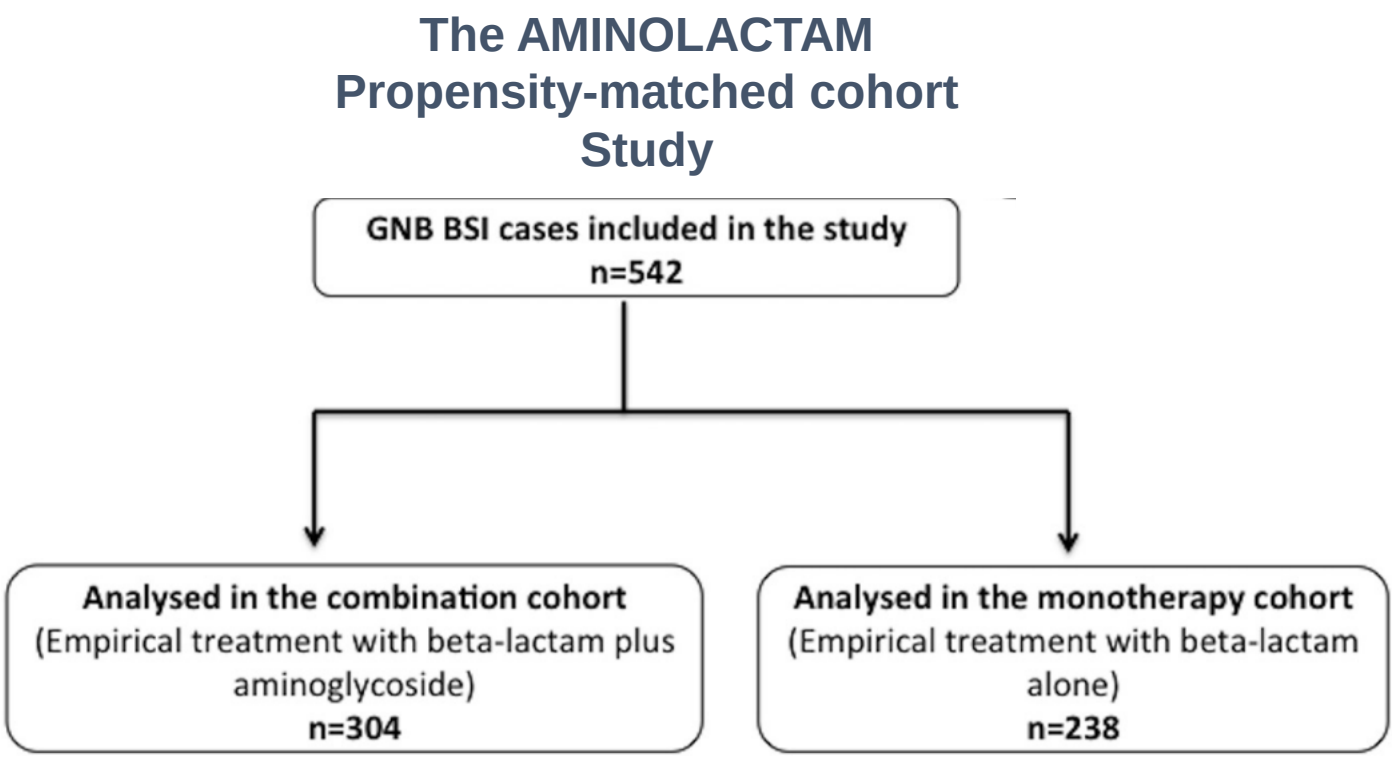
- Propensity-score matched multi-center cohort
- BSIs due to CPE

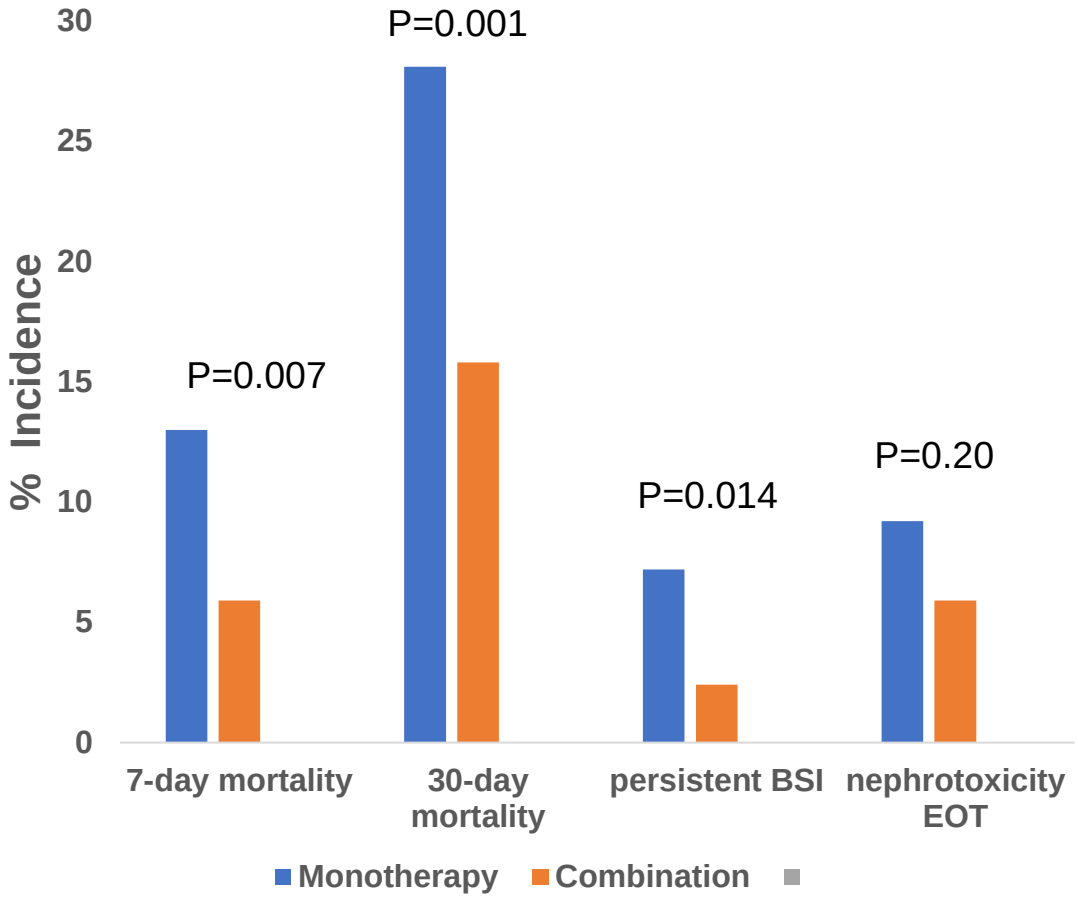




Gutiérrez-Gutiérrez B, et al. Lancet Infect Dis. 2017;17(7):726-734.

Combination treatment in neutropenia



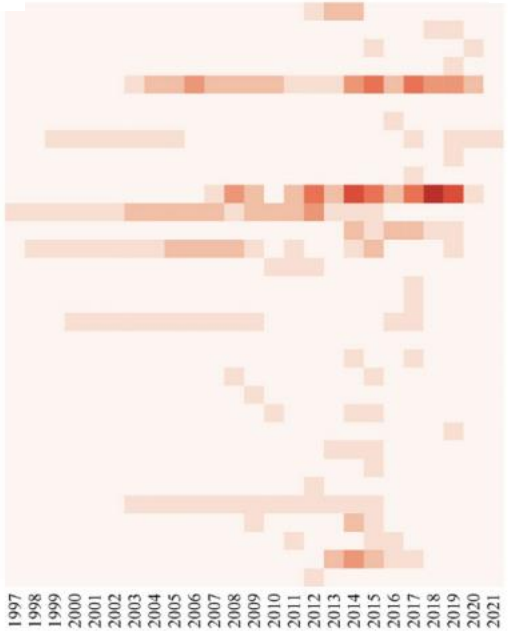


Albasanz-Puig et al (AMINOLACTAM Study). Antimicrob Agents Chemother. 2021;65(8):e0004521.

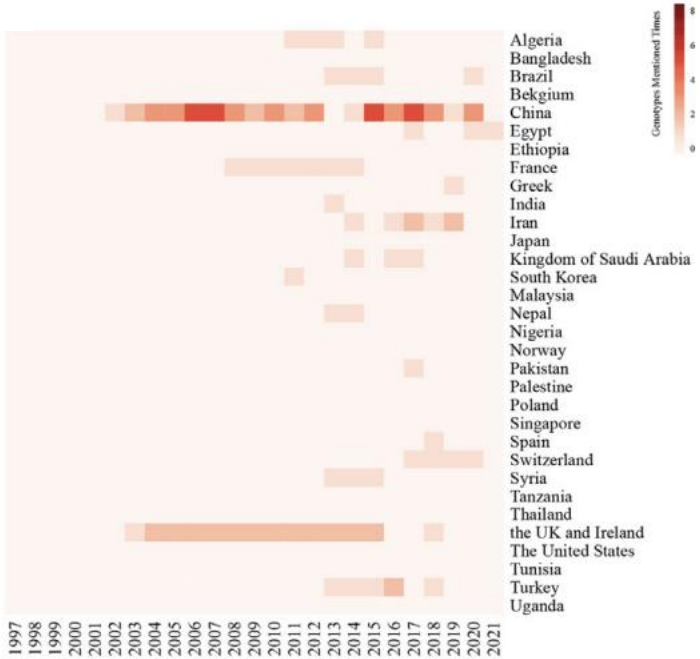
Resistance to aminoglycosides

- Enzymatic drug modification/ AME (aminoglycoside-modifying enzymes)
  - N-acetyl-transferases
  - O-nucleotidyl-transferases
  - O-phosphorylo-transferases
- 16S rRNA methylation
  - armA
  - rmtB
- Efflux pumps
  - MexXY-OprM system for P. aeruginosa
- Plasmid-mediated combined resistance
  - ESBLs
  - Carbapenemases

AME genotypes

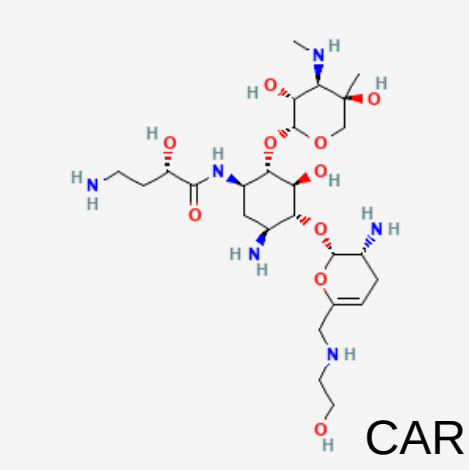


16S rRNA methylase genotypes



Krause KM, et al. Cold Spring Harb Perspect Med. 2016;6(6):a027029.
Zhang Y, et al. Biosaf Health. 2023;5(1):14-20. DOI: 10.1016/j.bsheal.2023.01.001

Plazomicin



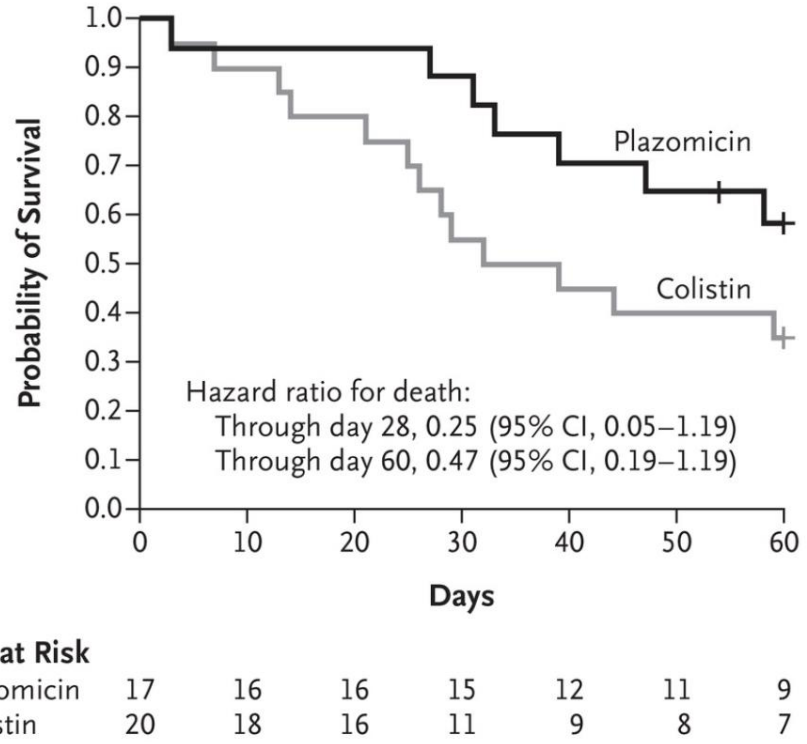
Dosing: single dose of 15mg/kg/day

EPIC study: cUTI, including pyelonephritis

Time of Assessment and End Point	Plazomicin (N=191)	Meropenem (N=197)	Difference (95% CI)†
	number (percent)		*percentage points*
Day 5			
Primary end point: composite cure at day 5	168 (88.0)	180 (91.4)	−3.4 (−10.0 to 3.1)
Clinical cure	171 (89.5)	182 (92.4)	−2.9 (−9.1 to 3.3)
Microbiologic eradication	188 (98.4)	193 (98.0)	0.5 (−3.1 to 4.1)
End of intravenous therapy			
Composite cure	179 (93.7)	187 (94.9)	−1.2 (−6.5 to 4.0)
Clinical cure	184 (96.3)	190 (96.4)	−0.1 (−4.6 to 4.3)
Microbiologic eradication	186 (97.4)	192 (97.5)	−0.1 (−4.1 to 3.9)
Test-of-cure visit			
Primary end point: composite cure at 15 to 19 days after start of therapy	156 (81.7)	138 (70.1)	11.6 (2.7 to 20.3)
Clinical cure	170 (89.0)	178 (90.4)	−1.4 (−7.9 to 5.2)
Microbiologic eradication	171 (89.5)	147 (74.6)	14.9 (7.0 to 22.7)

Wagenlehner FME, et al. N Engl J Med. 2019;380(8):729-740.

CARE study: BSI, VAP, or HAP due to CRE

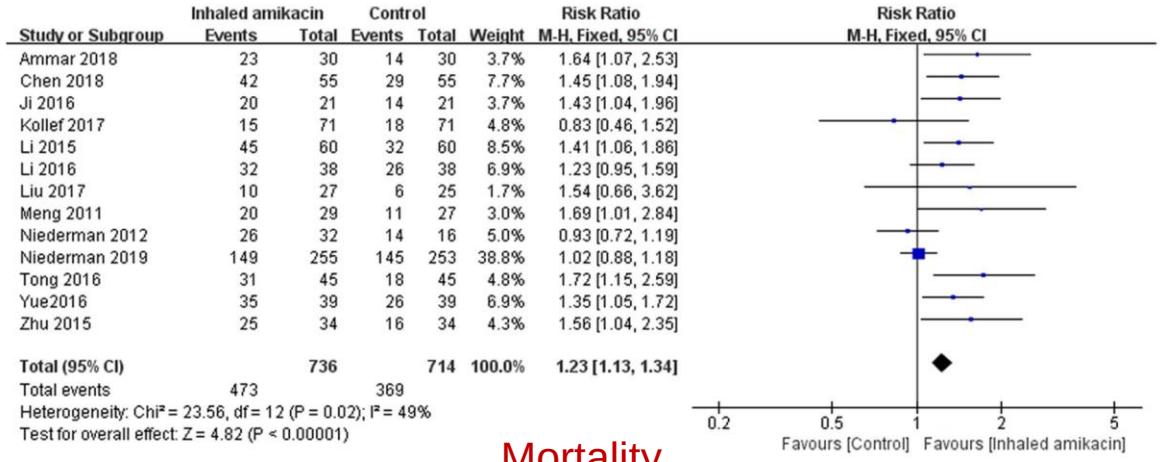


McKinnell JA, et al. N Engl J Med. 2019;380(8):791-793.

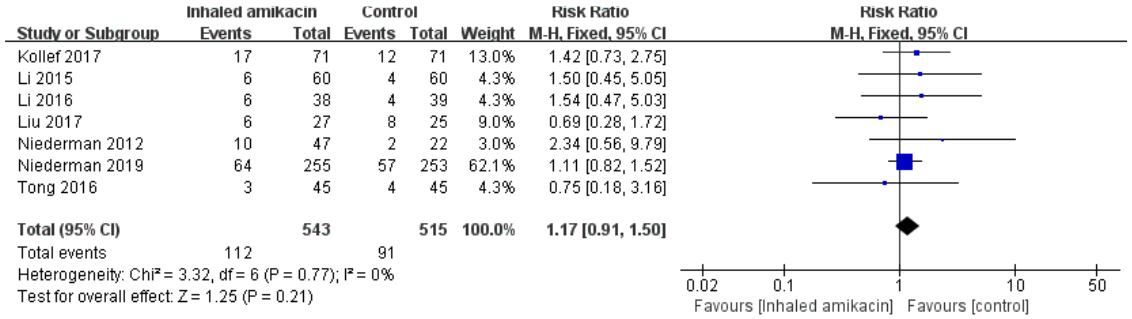
Nebulized dosing

- Infected site delivery
  - Higher exposure
  - Lower toxicity
- Meta-analysis for neb amikacin in Gram (-) pneumonia
  - 13 RCTs, 1733 adults
  - Better clinical response and microbiological eradication
  - No effect on mortality
  - **No solid data to support it**
- As prevention strategy among MV
  - Lower risk for VAP at 28 days
  - No difference in mortality

Clinical response



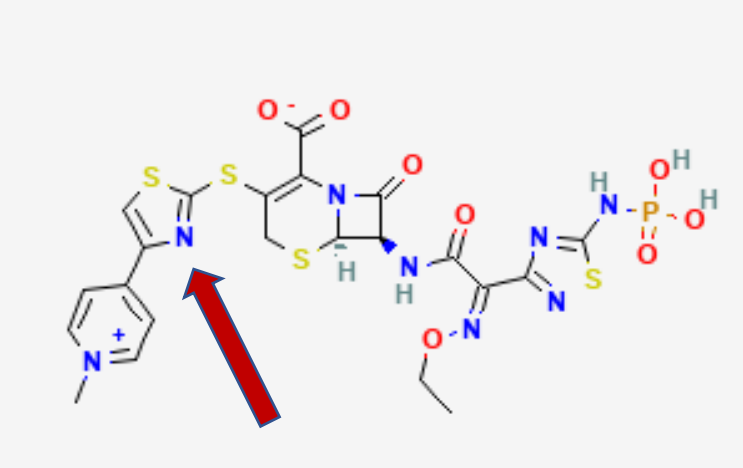
Mortality



Qin JP, et al. Sci Rep. 2021;11(1):6969.

Ehrmann S, et al. N Engl J Med. 2023. doi: 10.1056/NEJMoa231030

Ceftaroline



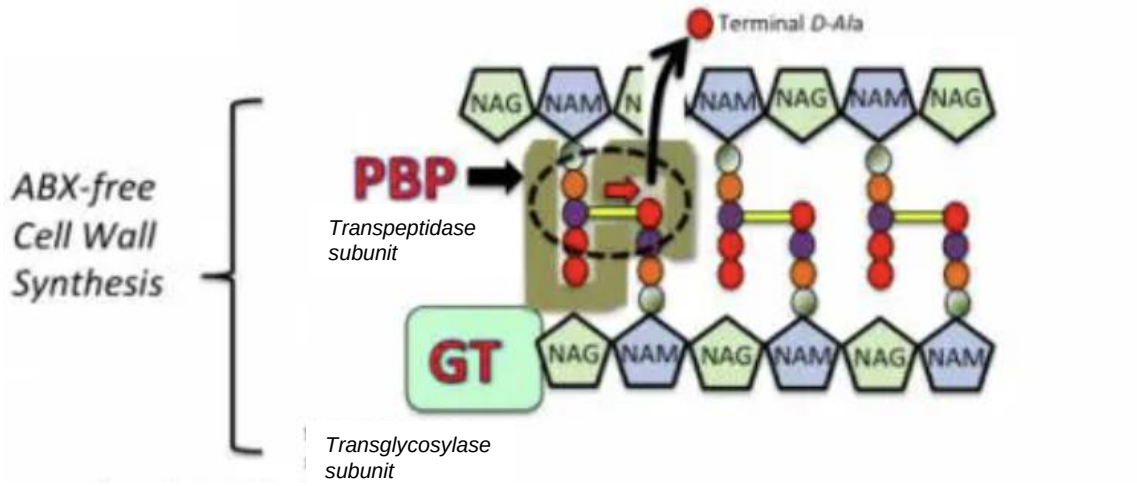
- 5th-generation cephalosporin
- Administered as prodrug (ceftaroline fosamil)
- Quickly hydrolysed to its active form, via plasma phosphatases
- Authorization for ABSSSI and CAP (2010 FDA, 2012 EMA)
- The only beta-lactam with activity against MRSA

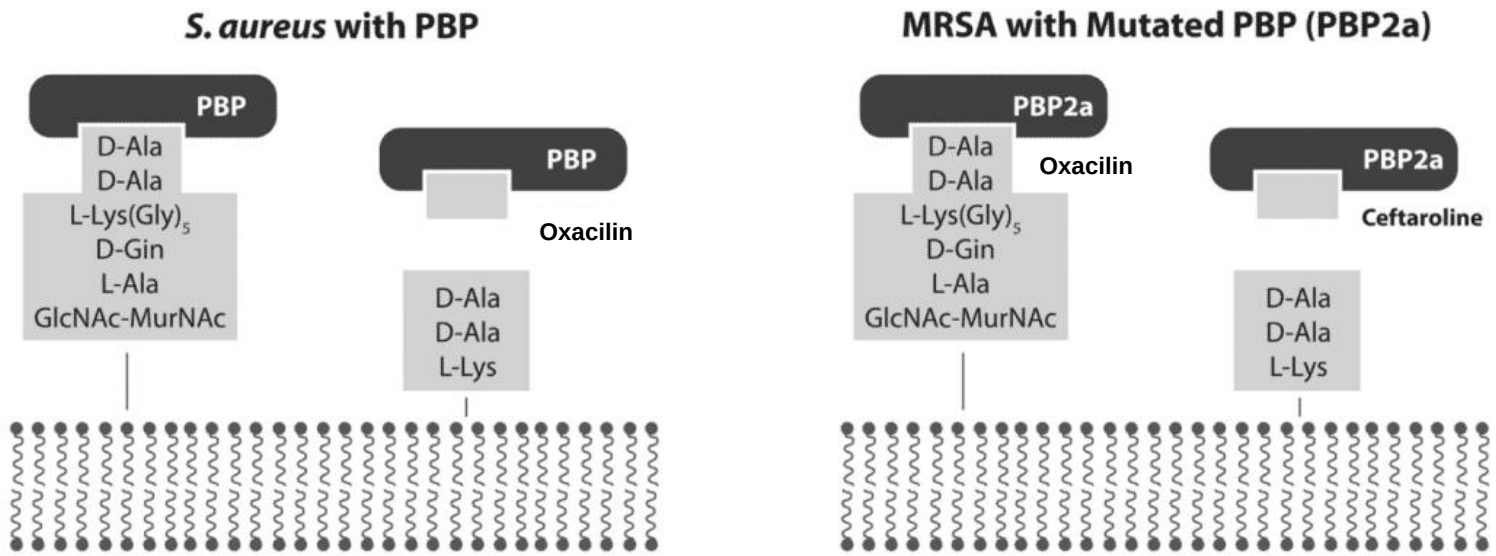
Carcione D et al. Pharmaceuticals (Basel). 2023;16(9):1304.
https://pubchem.ncbi.nlm.nih.gov/

Mechanism of action

- High affinity of ceftaroline for penicillin-binding proteins (PBPs), PBPs 1, 2, and 3 (staphylococci), PBP 2A (MRSA), PBPs 2X, 2A, 2B and 3 (Pen R pneumococci)

- Ability of ceftaroline to trigger a conformational change in PBP, causing the (normally shielded) active site to be exposed for binding



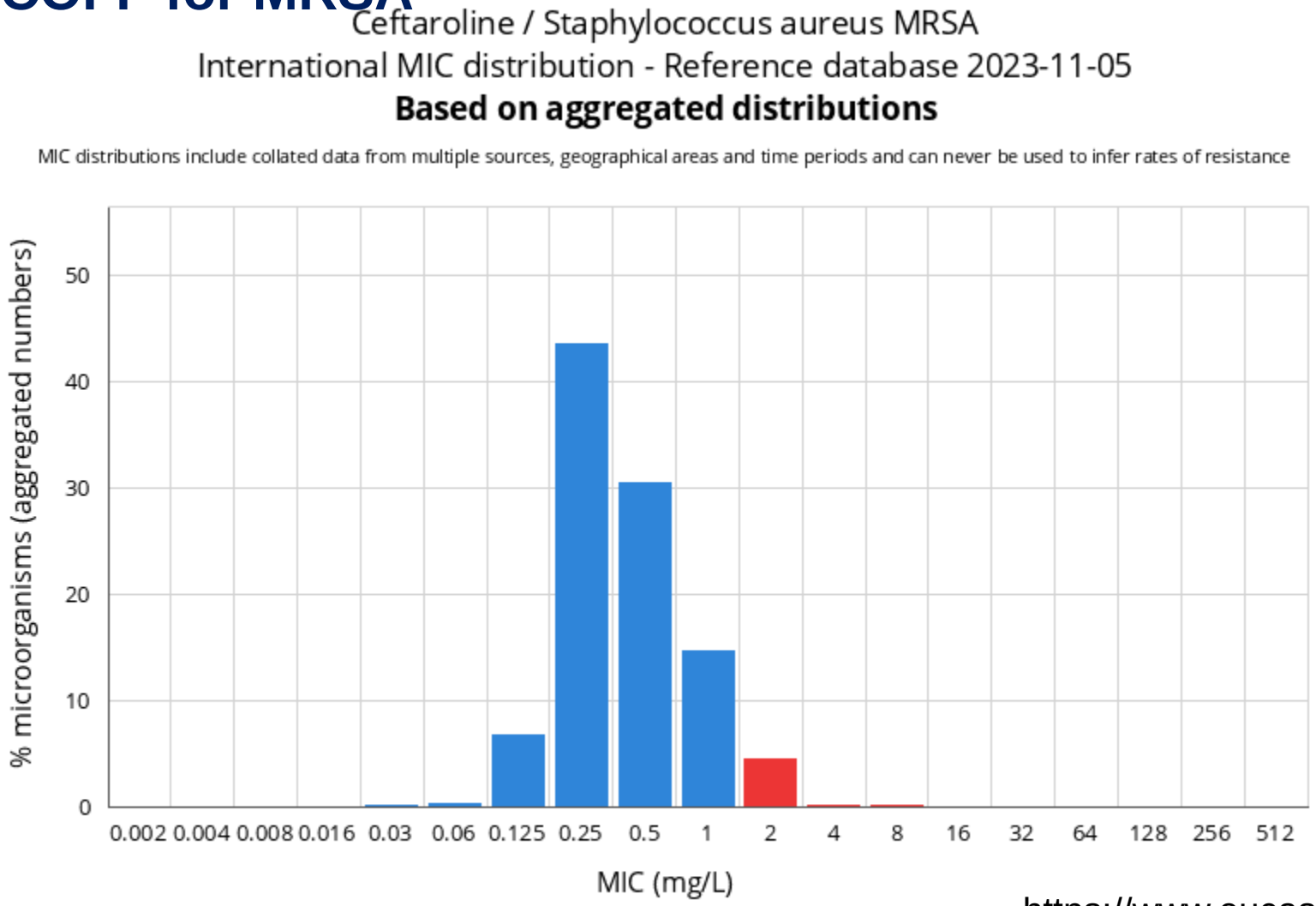


Duplessis C, et al. Clin Med Rev Ther. 2011;3:a2466.

Antimicrobial Spectrum		
Gram (+) bacteria		
Cocci	*Staphylococcus aureus*	Including MRSA, VISA, VRSA, LRSA
	Coagulase-negative staphylococci	
	Enterococcus faecalis (?)	**Not active against E. faecium**
	S. pneumoniae	Including Pen-I and -R
	S. pyogenes	
	Viridans group Streptococci	
Bacilli	*L. monocytogenes*	
Gram (-) bacteria		
	E. coli & K. pneumoniae	**Not if ESBL+, or Carba-producing**
	E. cloacae	
	P. mirabillis	
	S. marcescens	
	H. influenzae	Including β-lactamase producing
Anaerobic bacteria		
	P. multocida	

Laudano JB. J Antimicrob Chemother. 2011;66 Suppl 3:iii11-8.

MIC and ECOFF for MRSA



https://www.eucast.org/clinical_breakpoints

MIC
Epidemiological cut-off (ECOFF): (1) mg/L
Wildtype (WT) organisms: ≤ 1 mg/L

Confidence interval: 0.25 - 2
10181 observations (3 data sources)

PK/PD profile

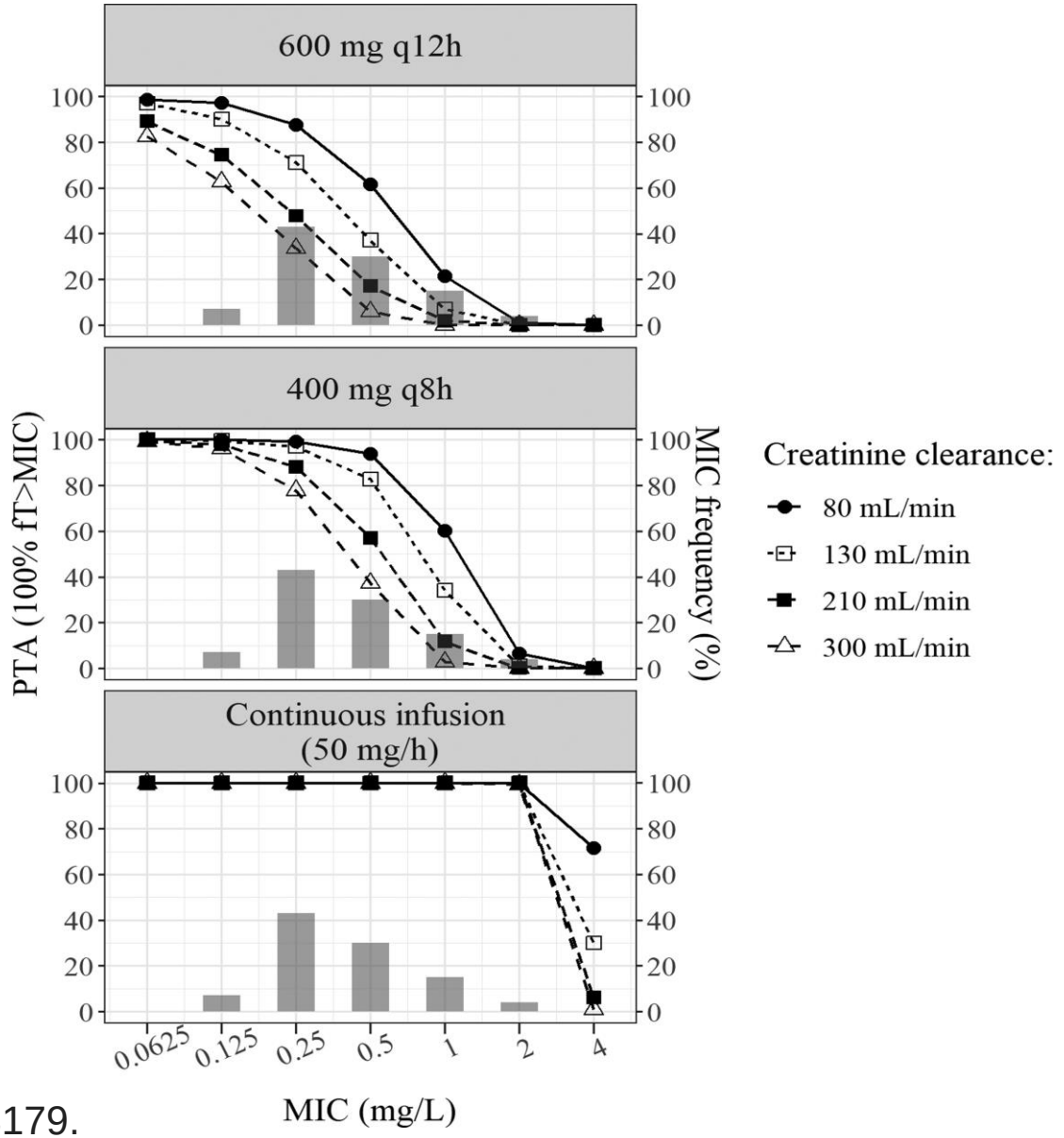
- $T_{1/2}$ 2.6h
- Nearly exclusive renal clearance (up to 70% unchanged)
- Lung penetration similar to other b-lactams (ELF/ plasma≈23%)
- Low penetration in CFS (6%→ 15% if inflammed meninges)
- Modest PAE (≈2h)

- Efficacy
  - Time that free drug concentrations remains above the MIC (fT > MIC): 100%
  - Alternatively: fT> 4*MIC: 100%

Chauzy A, et al. J Antimicrob Chemother. 2022;77(11):3173-3179.
Torres A, et al. Eur Respir Rev. 2023;32(170):230117.
Abate G, et al. Ann Pharmacother. 2022;56(12):1339-1348.

Dosing

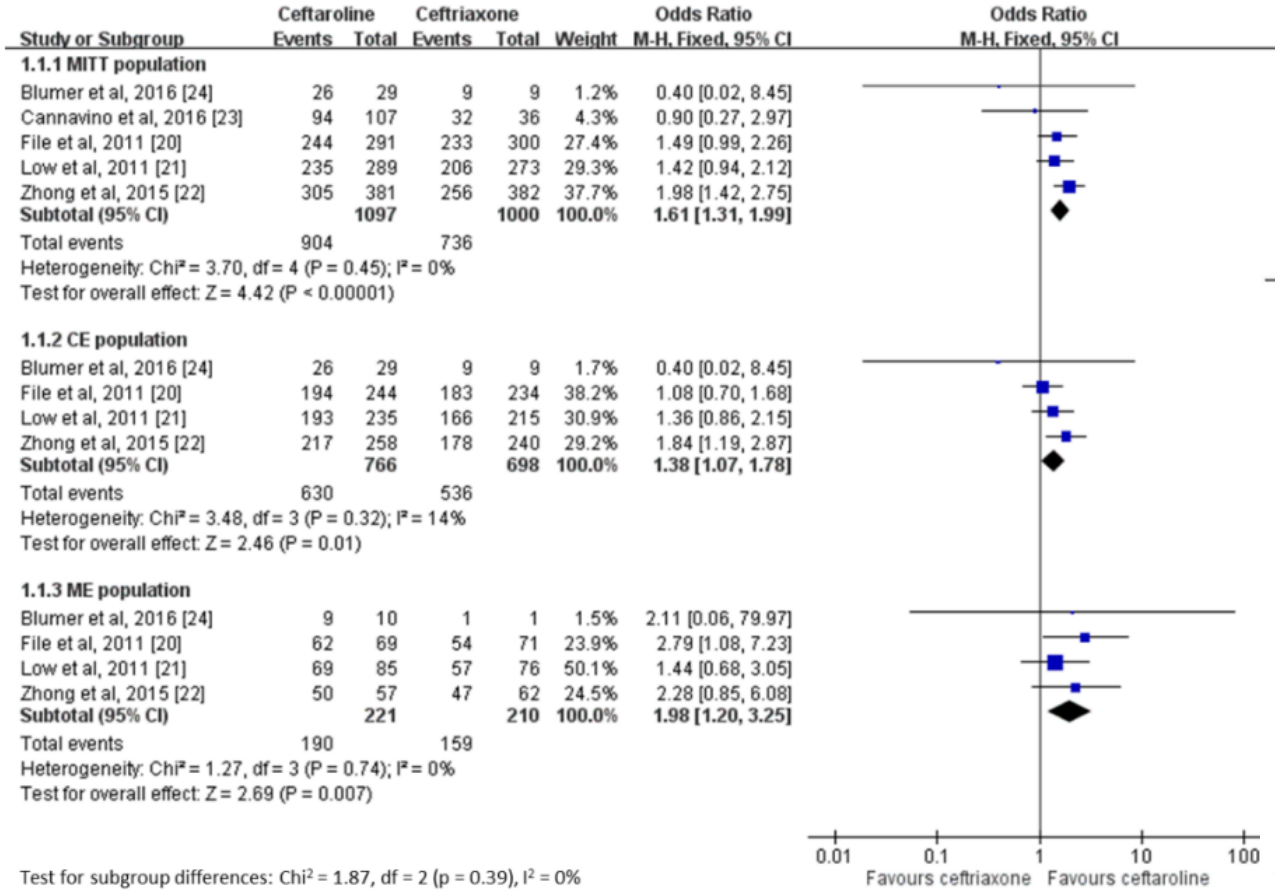
- Originally approved for 600 mg q12h (1h infusion)
- In critically ill patients or higher MICs 400 or 600 mg q8h (2h or 3-6h) may be required
- 24-hour continuous infusion (50mg/h) maybe an option
- Renal adaptation required in CL_{Cr} <50 ml/min
- Extensively removed during CRRT, doses should be increased



Chauzy A, et al. J Antimicrob Chemother. 2022;77(11):3173-3179.
Alarcia-Lacalle A, et al. Blood Purif. 2023;52(5):464-473.
Torres A, et al. Eur Respir Rev. 2023;32(170):230117.

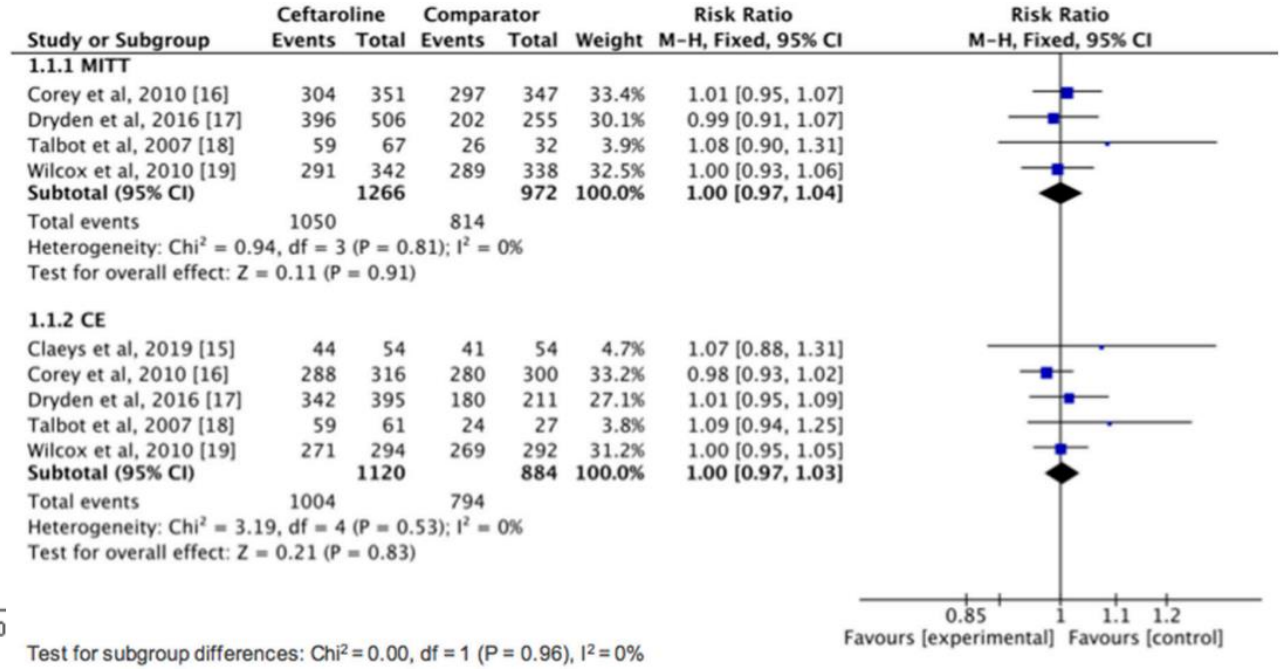
Trials and indications

CAP (vs ceftriaxone)



Lan SH, et al. J Clin Med. 2019;8(6):824.

ABSSSI (vs vanco/ aztreo)



Lan SH, et al. J Clin Med. 2019;8(6):776.

Off-label uses of ceftaroline

Infections caused by MRSA	N	Clinical success, n (%)
Bone and Joint infection	158	138 (87.3)
Endovascular infection	77	55 (71.4)
Bacteremia	177	142 (80.2)
Diabetic foot	201	163 (81.1)
HAP	110	87 (79)
Meningitis	0	5 (83)
Other*	30	20 (66.7)

*uveitis/endophthalmitis, urinary tract infection, prostatitis

Abate G, et al. Ann Pharmacother. 2022;56(12):1339-1348.
Pani A, et al. Int J Antimicrob Agents. 2019;54(5):562-571.

Toxicity

- The most common adverse events in the CANVAS trials: nausea (5.9%), headache (5.2%), diarrhea (4.9%), pruritus (3.5%), rash (3.2%), generalized pruritus (2.2%), and dizziness (2.0%).
- The most common adverse events in the FOCUS trials: diarrhea (4.2%), headache (3.4%), insomnia (3.1%), and phlebitis (2.8%).
- Transaminase increase 2-3%
- Neutropenia up to 4% (caution if treatment exceeds 14 days)
- Eosinophilia (/ eosinophilic pneumonia) 2%

- C. difficile colitis 2%

Chauzy A, et al. J Antimicrob Chemother. 2022;77(11):3173-3179.
Alarcia-Lacalle A, et al. Blood Purif. 2023;52(5):464-473.
Torres A, et al. Eur Respir Rev. 2023;32(170):230117.

Resistance

- A total of 14 adults, 6 from the United States, 5 from Europe, and 3 from Asia, have been reported to have infections caused by ceftaroline-resistant MRSA
- The most common genetic changes were in PBP2A, including
  - Glu447Lys in 6 isolates,
  - Glu239Lys in 5 isolates
  - Tyr446Asn in 2 isolates
  - most of them conferred increase in IC_{50} but a combination is required for high-level resistance
- In 3 patients, no prior exposure to ceftaroline was identified

- In children, 6 out of 201 (3%) cilincal isolates had MRSA-resistance
- None of the subjects with a ceftaroline RS isolate experienced prior ceftaroline use.
- 5 out of 6 strains belonged to clonal complex (CC) 5/ ST5
- Existence of PBP and non-PBP mutations

Abate G, et al. Ann Pharmacother. 2022;56(12):1339-1348
McNeil JC, et al. Antimicrob Agents Chemother. 2022;66(10):e0074522.