La terapia antinfettiva personalizzata nel paziente critico

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- MSD
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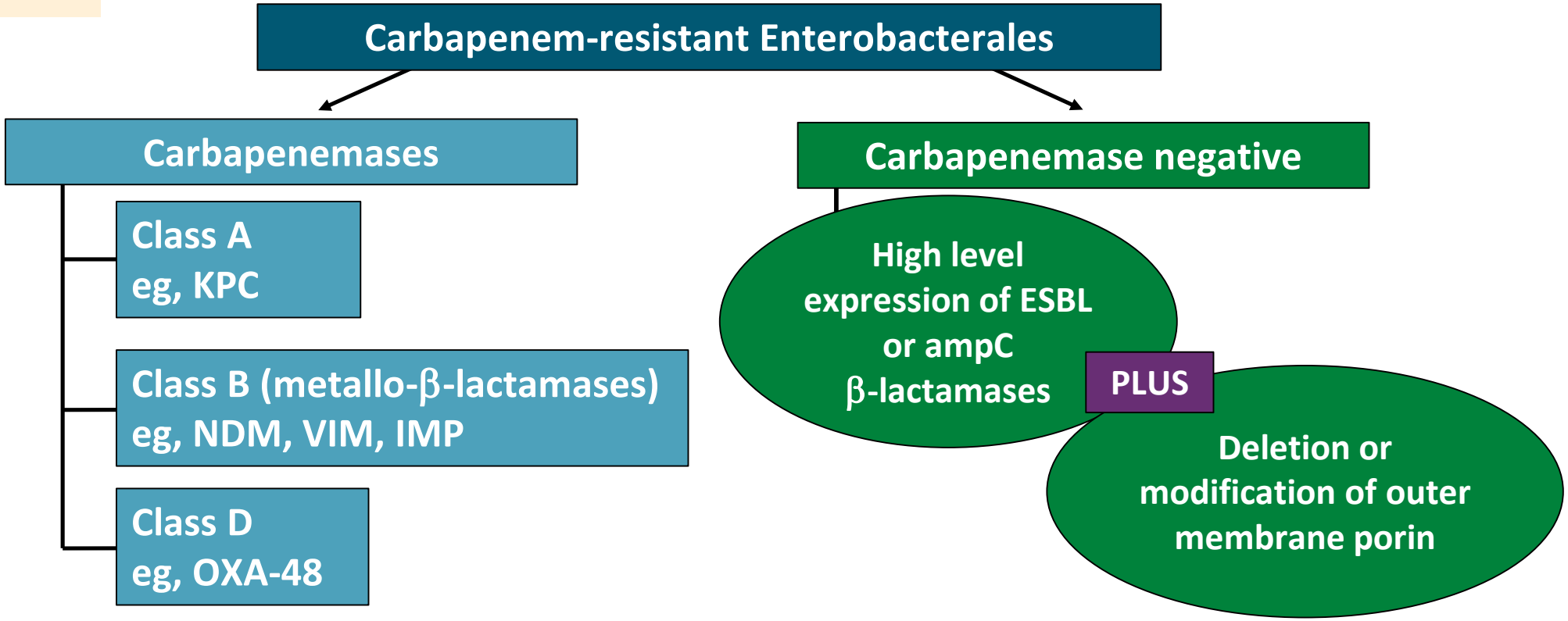
- ViiV

CRE Resistance Mechanisms

CRE ≠ KPC



cdc.gov/hai/organisms/cre/technical-info.html. Tamma. Clin Infect Dis. 2021;72:1109. Nordmann. Clin Infect Dis. 2019;69:S521.

Attività in vitro dei nuovi antibiotici

Antibiotico	*Enterobacterales*					
	Carbapenemasi di classe A (es. KPC)	Carbapenemasi di classe B (es. NDM)	Carbapenemasi di Classe D (es. OXA-48)	*Pseudomonas aeruginosa*	*Acinetobacter baumannii*	*Stenotrophomonas maltophilia*
Ceftobiprolo						
Ceftolozano-tazobactam						
Ceftazidima-avibactam						
Cefiderocol						
Meropenem-vaborbactam						
Imipenem-relebactam						
Aztreonam-avibactam						
Plazomicina						
Eravaciclina						

IMP: imipenemasi. **KPC**; *Klebsiella pneumoniae* carbapenemasi. **MBL**: metallo-β-lattamasi. **MDR**: multiresistente. **NDM**: New Delhi metallo-β-lattamasi. **OXA-48**: oxacillinasi-48. **VIM**: Verona Integron metallo-β-lattamasi.

1. Kirkegaard-Biosca C, et al. Antibiotics (Basel). 2024;13(9):874. **2.** Bassetti M, et al. Eur Respir Rev. 2022;31(166):220119.

MBL-Producing Enterobacterales: Potential Treatment Options for 2025 and Beyond

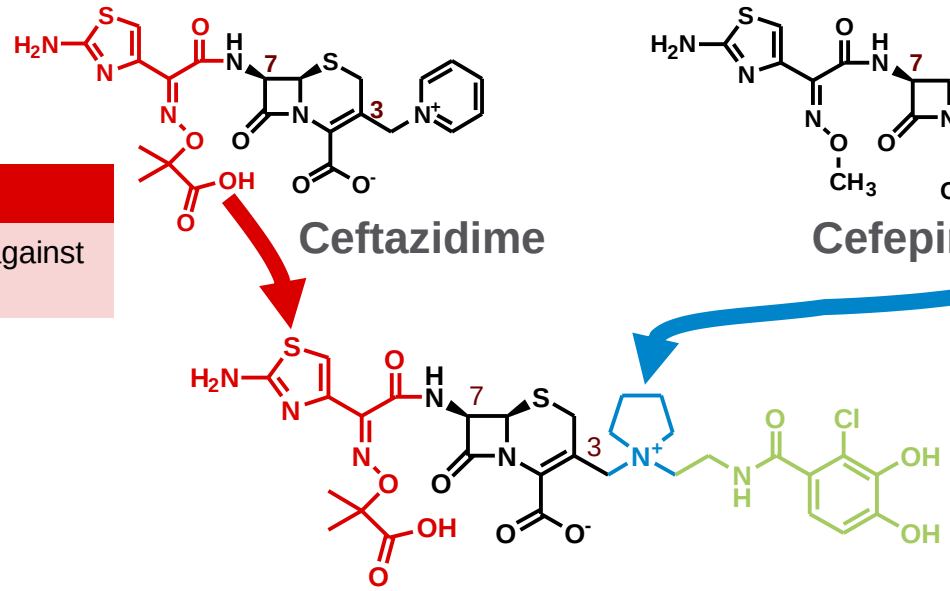
Aztreonam/ avibactam

Cefepime/ taniborbactam

Cefepime/ zidebactam

CEFIDEROCOL: unique structure

- Cefiderocol incorporates features of other cephalosporin antibiotics, but is distinct from other beta-lactam antibiotics due to its beta-lactamase resistance and iron chelation[1]



C-7 side chain[3]

- Enhances stability against beta-lactamases

C-3 side chain[2]

- Facilitates penetration of the Gram-negative outer membrane
- Confers low affinity for beta-lactamases

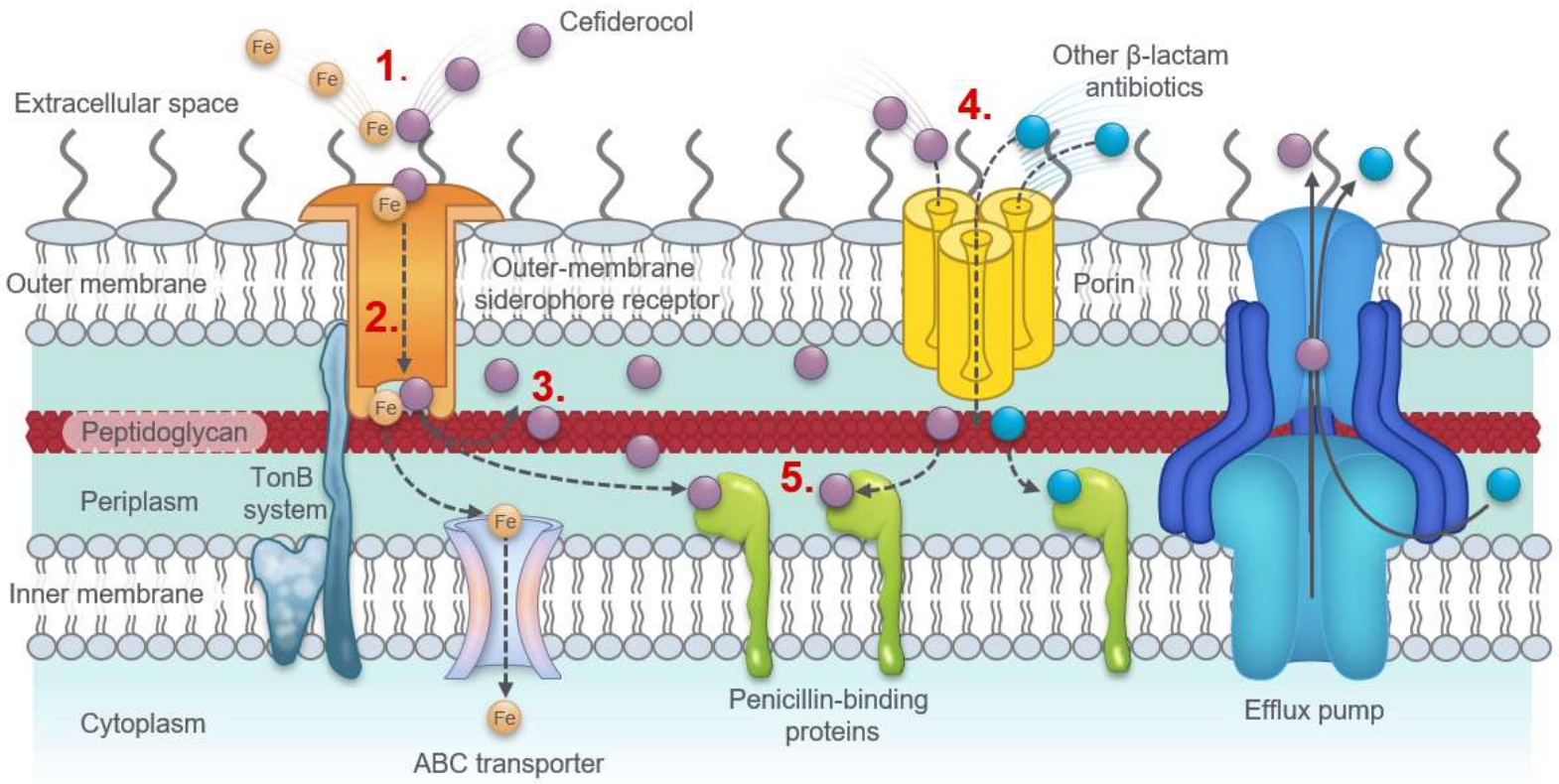
Catechol moiety

- Provides additional stability against beta-lactamases[4]
- Binds to free iron[5]

1. Ito A, et al. *Antimicrob Agents Chemother* 2016;60:7396–40; 2. Hancock RE, et al. *J Chemother* 1996;8 Suppl 2:31–6; 3. Craig WA et al. *Principles and Practice of Infectious Diseases (Eighth Edition)* 2015; Chapter 21:278–292; 4. Ito-Horiyama T, et al. *Antimicrob Agents Chemother* 2016;60:4384–6; 5. Ito A, et al. *J Antimicrob Chemother* 2016;71:670–7.

CEFIDEROCOL: unique mechanism of entry overcomes resistance mediated by changes to porin channels and efflux-pump overexpression

- Cefiderocol is actively transported across the outer membrane to periplasm via an iron-uptake mechanism[1,2]



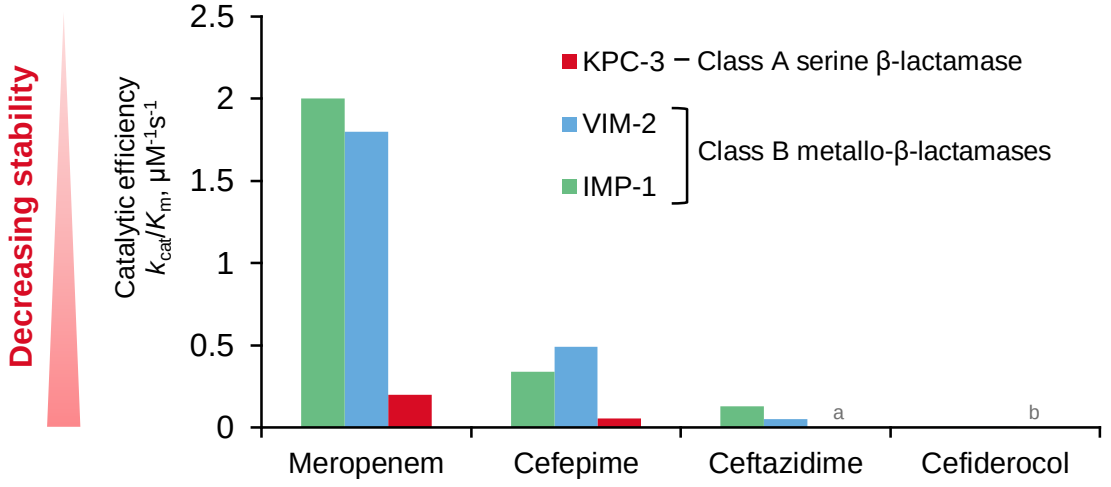
1. Chelation of extracellular iron
2. Chelated complex actively transported into periplasm by outer-membrane receptors
3. Iron ions dissociate
4. Cefiderocol also enters via diffusion through porins like other β-lactams
5. Cefiderocol binds and inhibits PBPs

PBP, penicillin-binding protein.

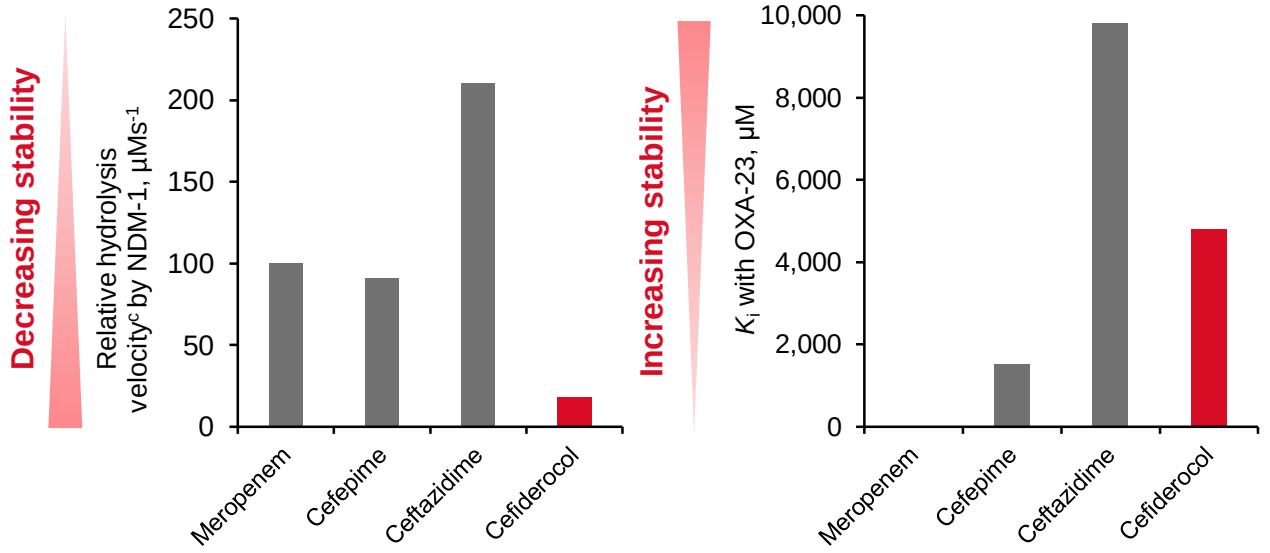
1. Ito A, et al. *Antimicrob Agents Chemother* 2016;60:7396–401; 2. Ito A, et al. *Antimicrob Agents Chemother* 2018;62:e01454–17

Cefiderocol is stable against various carbapenemases

Catalytic activity of some key carbapenemases against cefiderocol and comparators



Catalytic activity of NDM-1 (class B) and OXA-23 (class D) against cefiderocol and comparators



Cefiderocol's stability against carbapenemases enables it to overcome carbapenemase-mediated resistance

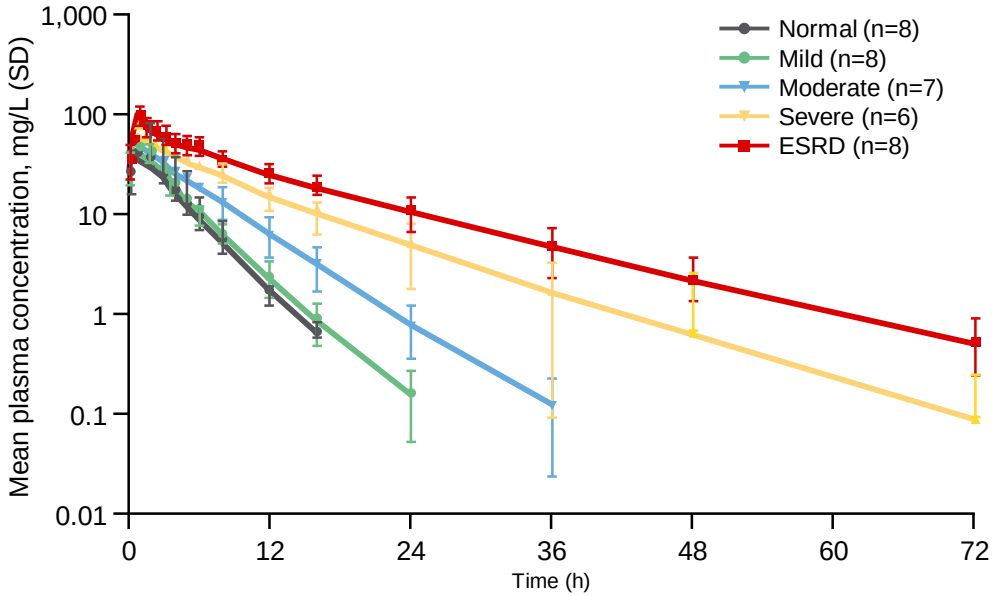
[a]Hydrolysis observed, but k_{cat} could not be determined because K_m was too high. [b]Slight hydrolysis of cefiderocol by KPC-3 was observed, but was too weak for calculation of k_{cat}.
[c]Calculated at a substrate concentration of 100 μM
k_{cat}, catalyst rate constant; K_i, inhibitor constant; K_m, Michaelis-Menten constant
Ito-Horiyama T, et al. *Antimicrob Agents Chemother.* 2016;60:4384–6

Impaired renal function requires dose modification to maintain cefiderocol plasma levels

PK of cefiderocol was assessed in patients with mild, moderate or severe renal impairment, or ESRD requiring haemodialysis, following 1 g intravenous 1-h infusion (N=38)[1]

- Cefiderocol is primarily eliminated by the kidneys[2]
- Therefore, cefiderocol elimination is dependent on renal function[1]
- Impaired clearance will cause **higher exposure** to cefiderocol[1]
- The plasma-protein-unbound fraction was similar across renal subgroups[1]

Mean plasma concentrations of cefiderocol following single-dose administration[1]



ESRD, end-stage renal disease; PK, pharmacokinetic; SD, standard deviation

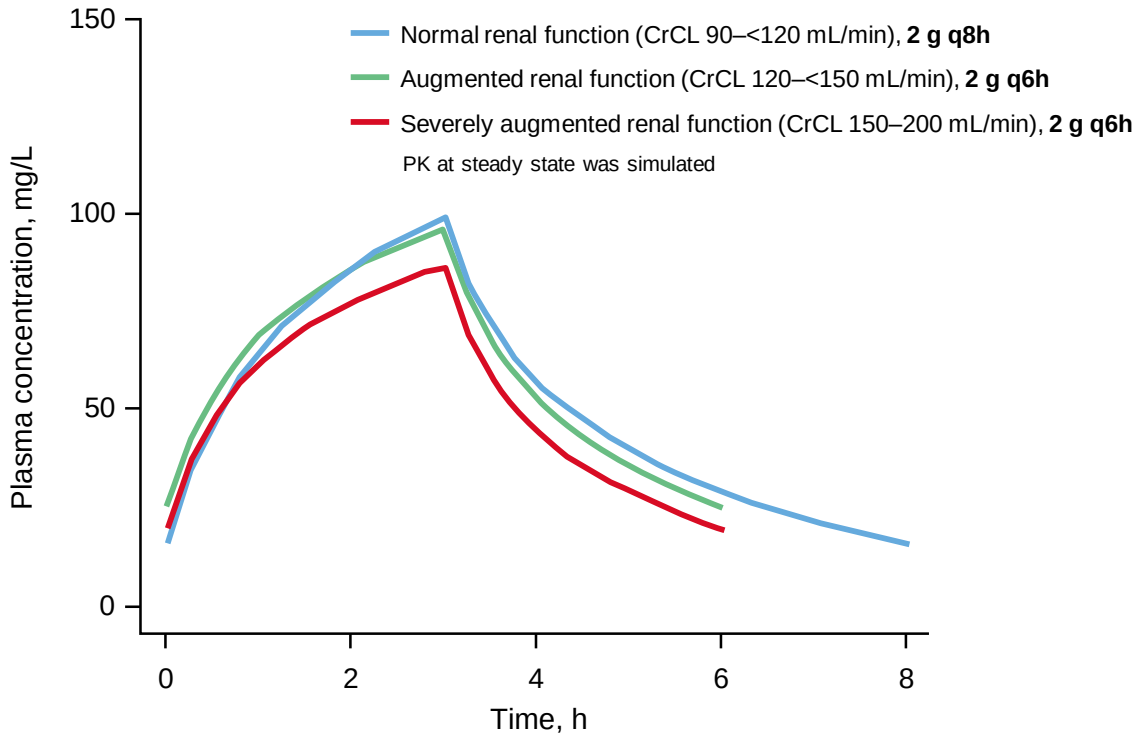
1. Katsube T, et al. *J Clin Pharm.* 2017;75:584–91; 2. Fetcroja® (cefiderocol). Summary of Product Characteristics. Shionogi B.V. 2025

Augmented renal clearance requires dose modification to maintain cefiderocol plasma levels

The target patient population for cefiderocol includes critically-ill patients with augmented renal clearance (CrCL >120 mL/min)[a1]

- Cefiderocol is primarily eliminated by the kidneys[2]
- Therefore, cefiderocol elimination is dependent on renal function[1]
- Augmented clearance will cause **lower exposure** to cefiderocol, affecting efficacy[1]
- For patients with augmented renal clearance, population PK modelling predicted infusion of cefiderocol 2 g q6h (versus q8h for normal renal function) over 3 h would provide >90% PTA versus target pathogens up to MIC of 4 mg/L[1]

Predicted plasma cefiderocol concentration profiles, following selected dosing regimens over 3-h infusion[3]



[a]Augmented renal clearance is characterised by increased creatinine clearance and elimination of renally cleared medications that could place patients at risk of therapeutic failure
CrCL, creatinine clearance; MIC, minimum inhibitory concentration; PK, pharmacokinetics; PTA, probability of target attainment; qnh, every n hour

1. Katsube T, et al. *Clin Infect Dis.* 2019; 69:s552–s8; 2. Fetcroja® (cefiderocol). Summary of Product Characteristics. Shionogi B.V. 2025;
3. Katsube T, et al. Presented at ECCMID 2015 (Poster P0251)

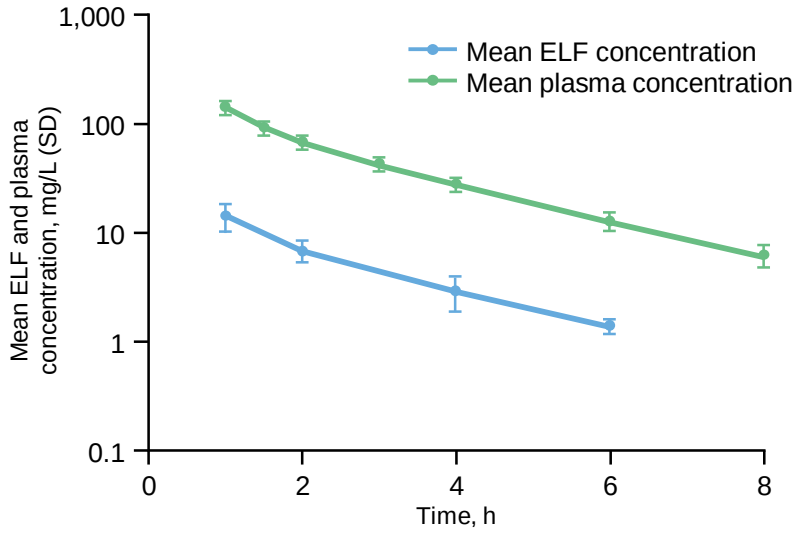
Cefiderocol ELF concentration profile was parallel to plasma concentration profile

Open-label study of cefiderocol concentrations in ELF and AM following 2 g 1-h infusion in healthy subjects (N=20)[1]

Key findings

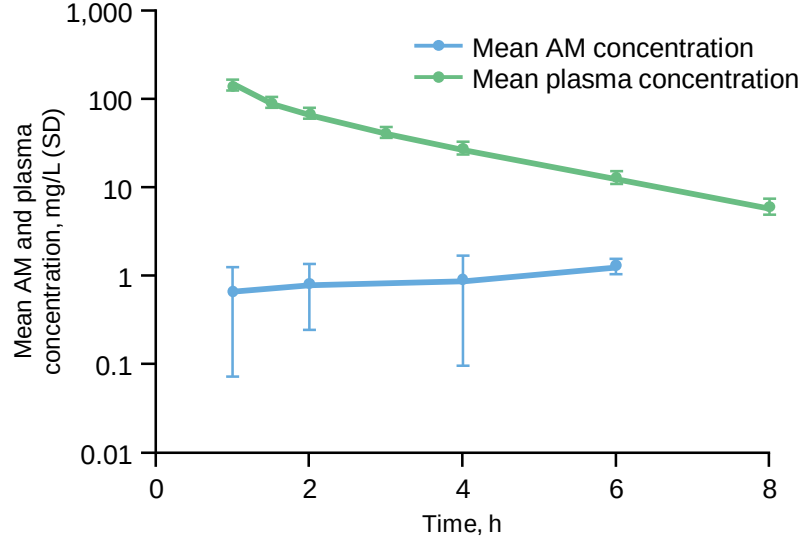
- Data suggest rapid distribution of cefiderocol from plasma to ELF[1]
- ELF concentrations are similar to other β-lactams used to treat respiratory infection[1]
- Evidence suggests that the concentration of cefiderocol in lung tissue will reach therapeutic levels; provides >95% PTA up to MIC of 2 mg/L[2]

Mean **ELF** and plasma concentrations of cefiderocol following single-dose administration[1]



ELF/plasma concentration ratio at 6 h = 12%

Mean **AM** and plasma concentrations of cefiderocol following single-dose administration[1]



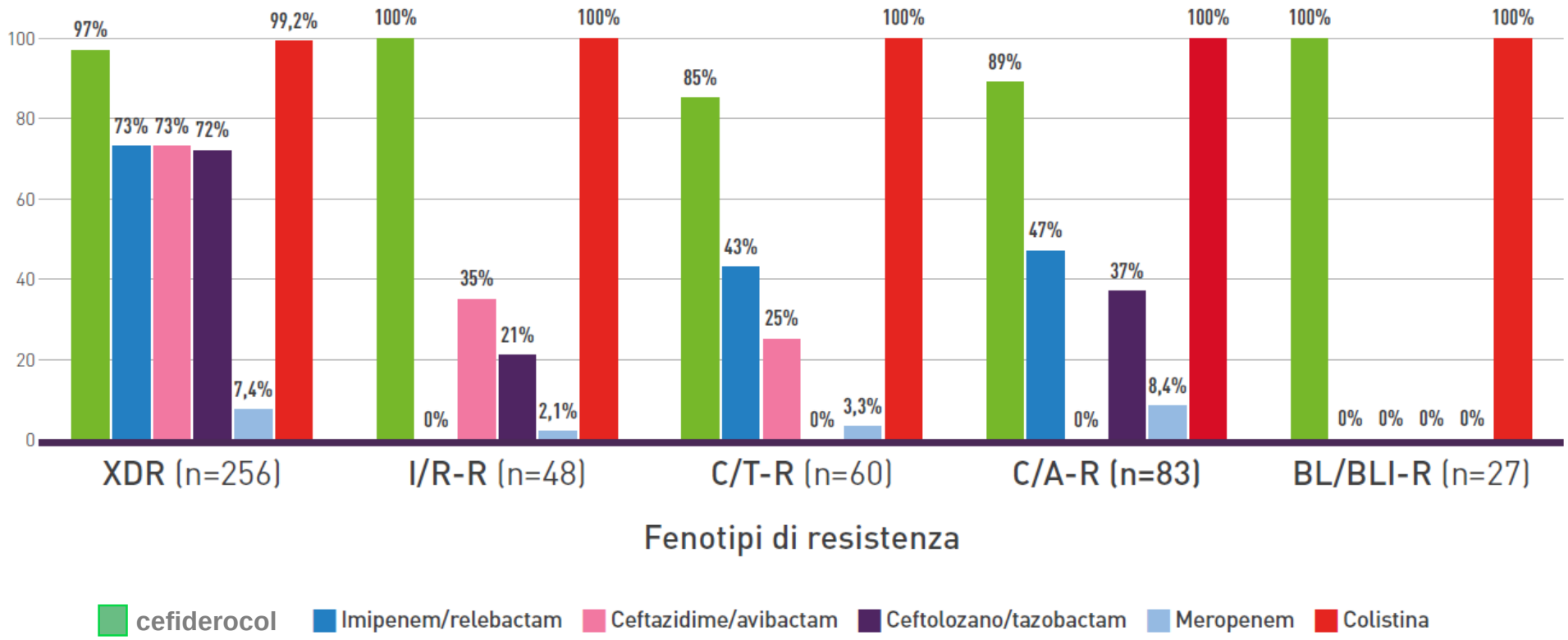
AM/plasma concentration ratio at 6 h = 10%

AM, alveolar macrophages; ELF, epithelial lining fluid; MIC, minimum inhibitory concentration; PTA, probability of target attainment; SD, standard deviation

1. Katsube T, et al. *J Antimicrob Chemother.* 2019;74:1971–74; 2. Kawaguchi N, et al. *J Clin Pharmacol.* 2022;62:670–80

Isolates with resistant phenotypes were more susceptible to cefiderocol than to comparators

Antimicrobial activity of cefiderocol and comparator tested on 2.282 isolates of *PA*



PA isolates already resistant to a BL-BLI combination have a greater probability of developing resistance to another BL-BLI, while maintaining susceptibility to cefiderocol
11%-14% treatment emergent resistance has been reported after patient were treated with C/T

Based on EUCAST susceptibility breakpoints (Fetcroja: ≤2 mg/L; ceftazidime/avibactam: ≤8 mg/L; ceftolozane/tazobactam: ≤4 mg/L; imipenem/relebactam: ≤ 2 mg/L; meropenem/vaborbactam: ≤8 mg/L)

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

C/T-R, ceftolozane/tazobactam-resistant; CZA-R, ceftazidime/avibactam-resistant; IMR-R, imipenem-resistant; MEM-R, meropenem-resistant; MVB-R, meropenem/vaborbactam-resistant

2024 IDSA Guidance: CRE

New CLSI recommendation to test for carbapenemases for CRE isolates

Resistance	Preferred	Alternative Options
KPC	▪ Meropenem/vaborbactam ▪ Ceftazidime/avibactam ▪ Imipenem/cilastatin/relebactam	▪ Cefiderocol ▪ Tigecycline or eravacycline – Not recommended for treatment of UTIs or BSIs
NDM, VIM, IMP	▪ Ceftazidime/avibactam + aztreonam ▪ Cefiderocol	▪ Tigecycline or eravacycline – Not recommended for treatment of UTIs or BSIs
OXA-48-like	▪ Ceftazidime/avibactam	▪ Cefiderocol

Tamma. Clin Infect Dis. 2024;ciae403. clsi.org/meetings/ast-file-resources/.

Ceftazidime/Avibactam + Aztreonam for MBLs: Additional Considerations

Based on results from surveillance studies, 90%-100% of MBL-producing isolates display susceptibility to ATM/AVI

Case reports of resistance to CZA + ATM due to mutations in PBP3 (reduces ATM binding)

Most clinical labs do not provide susceptibility testing results to this combination, so taking a leap of faith

Tamma. Clin Infect Dis. 2024;ciae403. Lodise. Antimicrob Agents Chemother. 2022;66:e0093622.

Ceftazidime/Avibactam + Aztreonam for MBLs

- Observational studies show benefit to ceftazidime/avibactam + aztreonam vs alternate therapies for MBL-producing infections

Study (Time Frame)	30-Day Mortality, % (n/N)	
	CZA + ATM	Alternative Therapies
Falcone 2021 (Nov 2018 - Dec 2019)	19 (10/52)	44 (22/50)
Falcone 2024 (Jan 2019 - Oct 2022)	22 (48/215)	30 (29/96)

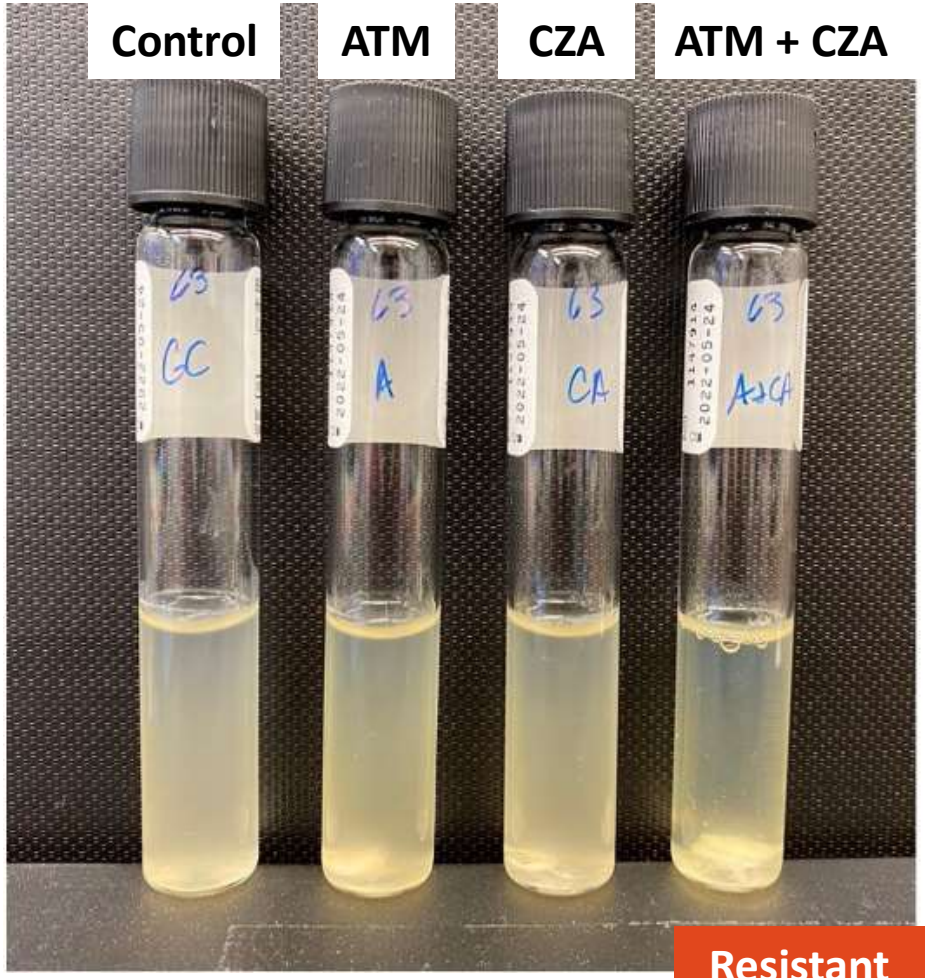
Dosing and Monitoring

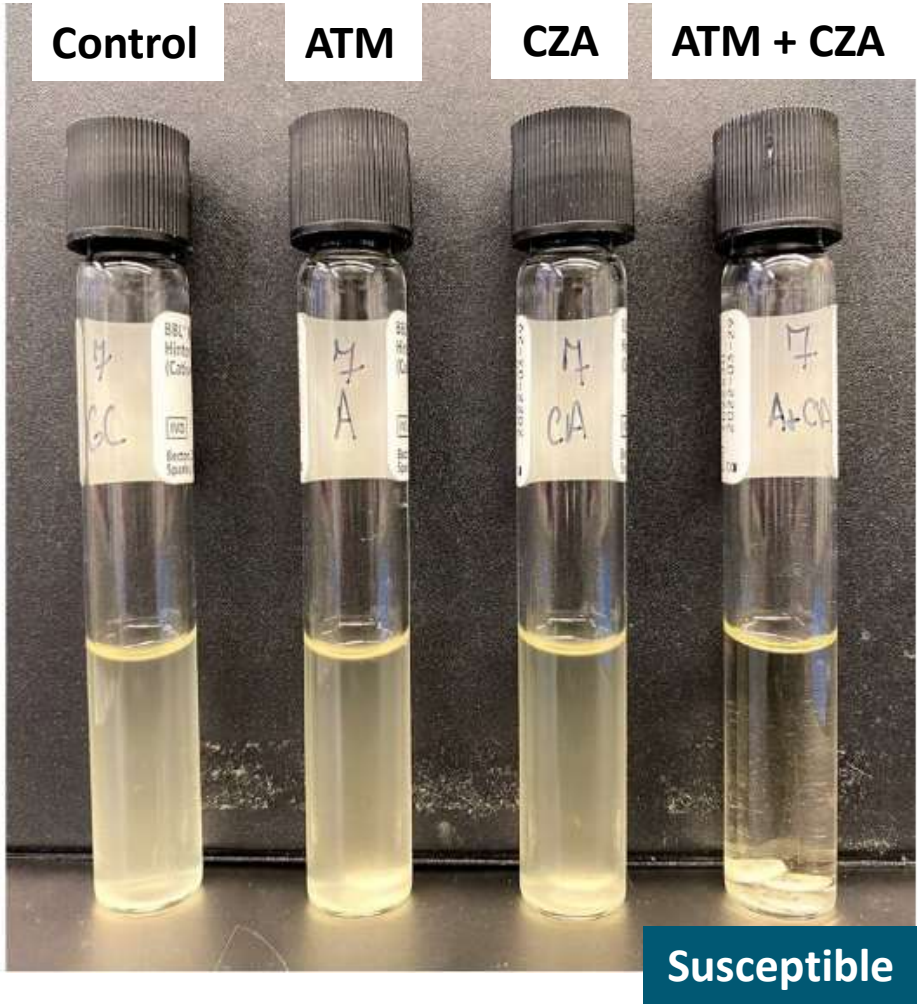
- Administer ceftazidime/avibactam + aztreonam together using Y-site administration, if possible
  - CZA: 2.5 g IV Q8 hr over 3 hr
  - ATM: 2 g IV Q8 hr over 3 hr
- Monitor LFTs
  - COMBINE: AST/ALT increase common in phase I trial, likely related to high doses of ATM

Falcone. Clin Infect Dis. 2021;72:1871. Falcone. Clin Infect Dis. 2024;78:1111.
Tamma. Clin Infect Dis. 2024;ciae403. Lodise. Antimicrob Agents Chemother. 2022;66:e0093622.

Ceftazidime/Avibactam + Aztreonam: Determining Susceptibility With Disk Elution Method

- Endorsed by CLSI
- Labs can now validate





Harris. J Clin Microbiol. 2023;61:e0164722. Doi: 10.1128/jcm.01647-22.

Cefiderocol for MBLs: Additional Considerations

Among patients with CR-infections, higher 28-day mortality observed with FDC vs BAT in CREDIBLE-CR (33% vs 16%)

- **APEKS-NP: no difference in mortality compared with meropenem for carbapenem-resistant infections**

Potential for inaccurate AST results

- **Requires a tight range of iron depletion for Mueller-Hinton Broth**

PBP3 mutations can confer cross resistance to cefiderocol

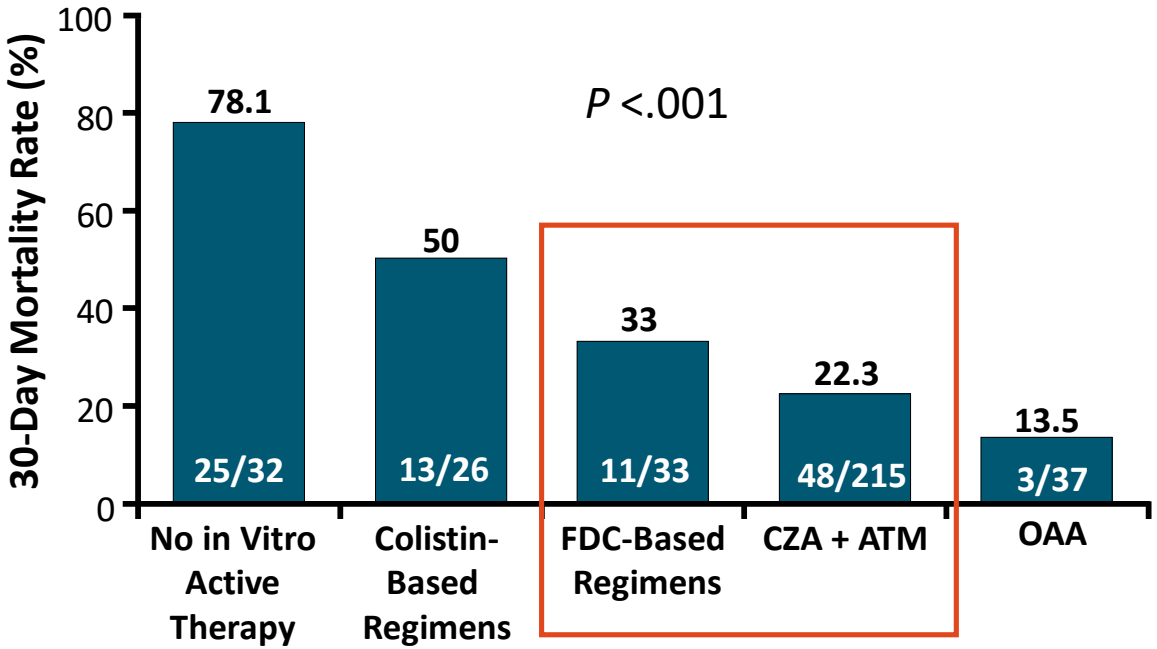
Bassetti. Lancet Infect Dis. 2021;21:226. Wunderink. Lancet Infect Dis. 2021;21:213.
Simner. J Clin Microbiol. 2023;61:e016022. Haidar. JAC Antimicrobi Resist. 2024;6:dlae141.

Cefiderocol for MBLs

- **SIDERO-WT Surveillance:** 91.5% of 211 MBL-producing Enterobacterales (NDM: 85.4%) susceptible to cefiderocol
- **CREDIBLE-CR and APEKS-NP:** pooled analysis from 2 phase III trials of 34 patients with MBL-producing CRE infections

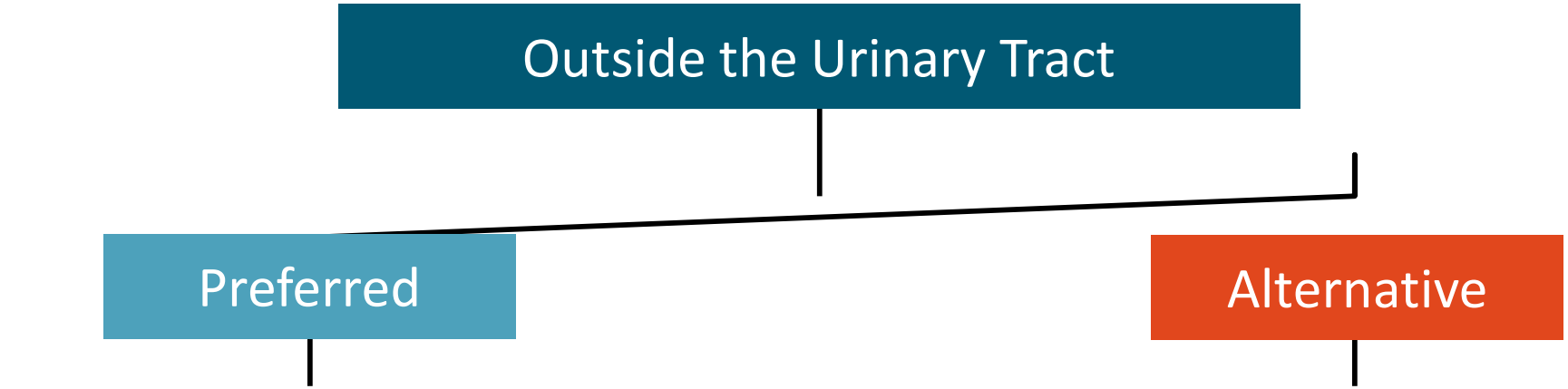
Outcome, %	Cefiderocol (n = 24)	Comparator (n = 10)
Clinical cure	71	40
Microbiologic cure	58	30
28-day all-cause mortality	13	50

- Prospective, observational study of MBL-producing Enterobacterales infections from Italy (N = 343)



Wise. Microb Drug Resist. 2023;29:360. Tamma. Clin Infect Dis. 2024;ciae403. Timsit. Clin Infect Dis. 2022;75:1081. Falcone. Clin Infect Dis. 2024;78:1111.

2024 IDSA Guidance: DTR-*P. aeruginosa*



For MBL-producing *P. aeruginosa,* cefiderocol is preferred

Tamma. Clin Infect Dis. 2021;72:109. O'Donnell. Pharmacotherapy. 2020;40:952.

Bassetti *et al. Antimicrobial Resistance & Infection Control* (2024) 13:91
https://doi.org/10.1186/s13756-024-01452-y

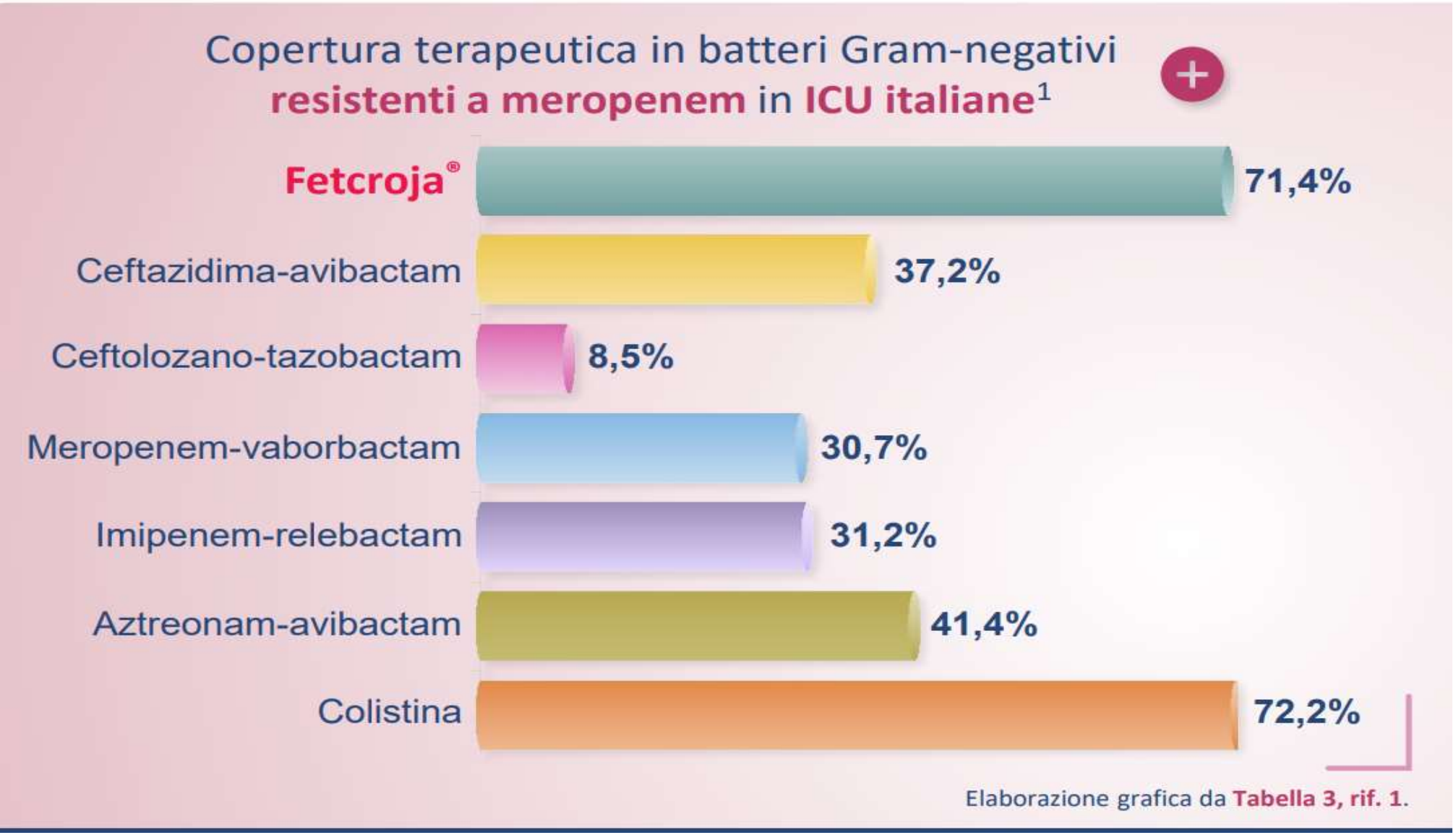
Antimicrobial Resistance &
Infection Control

RESEARCH Open Access

Predicting early appropriate therapy for patients infected by carbapenem-resistant Gram-negative pathogens in intensive care units in Italy

Matteo Bassetti[1], Gianpaola Monti[2], Anne Santerre Henriksen[3] and Christopher Longshaw[3*]

Results: The highest likelihood of susceptibility was reported for Colistin and CFDC



Bassetti et al, Antimicrobial Resistance & Infection Control (2024)

Fetcroja® è il primo e unico antibiotico ad aver ottenuto l'INNOVATIVITÀ da AIFA in considerazione di un VALORE TERAPEUTICO AGGIUNTO IMPORTANTE

Indicazione autorizzata: Fetcroja® è indicato per il trattamento delle infezioni dovute a organismi aerobi gram-negativi negli adulti con opzioni terapeutiche limitate (vedere paragrafi 4.2, 4.4 e 5.1).

Indicazione rimborsata SSN: La rimborsabilità Fetcroja® è limitata al trattamento di pazienti adulti ricoverati con infezioni gravi sostenute da:

AIFA AGENZIA ITALIANA DEL FARMACO

- Enterobacterales carbapenem resistant (CR) che producono metallo-beta-lattamasi (MBL);
- Pseudomonas aeruginosa che produce metallo-beta-lattamasi (MBL) e
- patogeni Gram-Negativi (GN) non fermentanti Difficult to Treat (DTR): Pseudomonas aeruginosa carbapenem resistant (CRPA), Acinetobacter baumannii carbapenem resistant (CRAB) e Stenotrophomonas maltophilia, in assenza di altre opzioni terapeutiche e secondo i principi di ottimizzazione dell'uso degli antibiotici.
L'utilizzo empirico è rimborsato solo nei casi di infezioni gravi, con evidenza clinica di sepsi, che mettano a rischio immediato la vita del paziente ed in cui non sia possibile il ricorso ad una circostanziata diagnosi microbiologica in tempi compatibili con l'avvio del trattamento, ma un'eziologia sostenuta dai suddetti batteri gram-negativi sia altamente probabile (per motivi clinici o epidemiologici)

Fetcroja®. Valutazione dell'innovatività Versione 1.0_CTS novembre 2022. Disponibile al link: https://www.aifa.gov.it/documents/20142/1851728/13_FETCROJA_scheda_innovativita_GRADE.pdf/48d6a12b-d664-7469-c938-db15a8d26a3b (Ultimo accesso settembre 2023)
Elenco farmaci innovativi, AIFA. Disponibile al link: Innovative medicinal products | Italian Medicines Agency (aifa.gov.it) (Ultimo accesso settembre 2023)

Infect Dis Ther
https://doi.org/10.1007/s40121-024-01016-y

ORIGINAL RESEARCH

Use of Cefiderocol in Adult Patients: Descriptive Analysis from a Prospective, Multicenter, Cohort Study

Daniele Roberto Giacobbe · Laura Labate · Chiara Russo Artimagnella · Cristina Marelli · Alessio Signori · Vincenzo Di Pilato · Chiara Aldieri · Alessandra Bandera · Federica Briano · Bruno Cacopardo · Alessandra Calabresi · Federico Capra Marzani · Anna Carretta · Annamaria Cattelan · Luca Ceccarelli · Giovanni Cenderello · Silvia Corcione · Andrea Cortegiani · Rosario Cultrera · Francesco Giuseppe De Rosa · Valerio Del Bono · Filippo Del Puente · Chiara Fanelli · Fiorenza Fava · Daniela Francisci · Nicholas Geremia · Lucia Graziani · Andrea Lombardi · Angela Raffaella Losito · Ivana Maida · Andrea Marino · Maria Mazzitelli · Marco Merli · Roberta Monardo · Alessandra Mularoni · Chiara Oltolini · Carlo Pallotto · Emanuele Pontali · Francesca Raffaelli · Matteo Rinaldi · Marco Ripa · Teresa Antonia Santantonio · Francesco Saverio Serino · Michele Spinicci · Carlo Torti · Enrico Maria Trecarichi · Mario Tumbarello · Malgorzata Mikulska · Mauro Giacomini · Anna Marchese · Antonio Vena · Matteo Bassetti · CEFI-SITA investigators

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Demographics and clinical characteristics

Table 1 Demographic and clinical characteristics of adult patients treated with cefiderocol

Variables	No. of patients	%	95% CI
Previous therapy with cefiderocol	4/194	2.1	0.7–5.2
Monotherapy	0/194	0.0	0.0–1.8
Combination therapy	4/194	2.1	0.7–5.2
Previous antibiotic therapy other than cefiderocol	129/186	69.4	62.4–75.7
Previous piperacillin/tazobactam	85/186	45.7	38.6–53.0
Previous ceftazidime/cefepime	11/186	5.9	3.1–10.3
Previous ceftolozane/tazobactam	16/186	8.6	5.2–13.5
Previous carbapenems	56/186	30.1	23.8–37.0
Previous ceftazidime/avibactam	14/186	7.5	4.4–12.2
Previous meropenem/vaborbactam	1/186	0.5	0.0–2.7
Previous imipenem/relebactam	0/186	0.0	0.0–1.9
Previous polymyxins	5/186	2.7	1.1–6.0
Previous chemotherapy	23/197	11.7	7.7–16.9
Previous steroid therapy	65/187	34.8	28.0–41.9
Previous therapy with immunosuppressants	26/193	13.5	9.2–19.0
Previous major surgery	75/199	37.7	31.1–44.7
Previous isolation of CR-GNB	67/186	36.0	29.2–43.2
Previous CRE	37/186	19.9	14.6–26.2
Previous CRPA	9/186	4.8	2.4–8.9
Previous CRAB	27/186	14.5	10.0–20.3
Previous MBL-producing CR-GNB	17/186	9.1	5.4–14.1

Previous ABs therapy

Previous carbapenems	**30,1%**
Previous C/T	**8,6%**
Previous C/A	**7,5%**
Previous M/V*	**0,5%**
Previous I/R*	**0,0%**
Previous polymixins	**2,7%**

Previous isolation of CR-GNB

Previous CRE	**19,9%**
Previous CRPA	**4,8%**
Previous CRAB	**14,5%**
Previous MBLs	**9,1%**

FETCROJA® available since June 2021 in Italy - reimbursed

***M/V: available since March 2021 in Italy -reimbursed**
***I/R: available since May 2022 in Italy -reimbursed**

Demographics and clinical characteristics

Table 1 Demographic and clinical characteristics of adult patients treated with cefiderocol

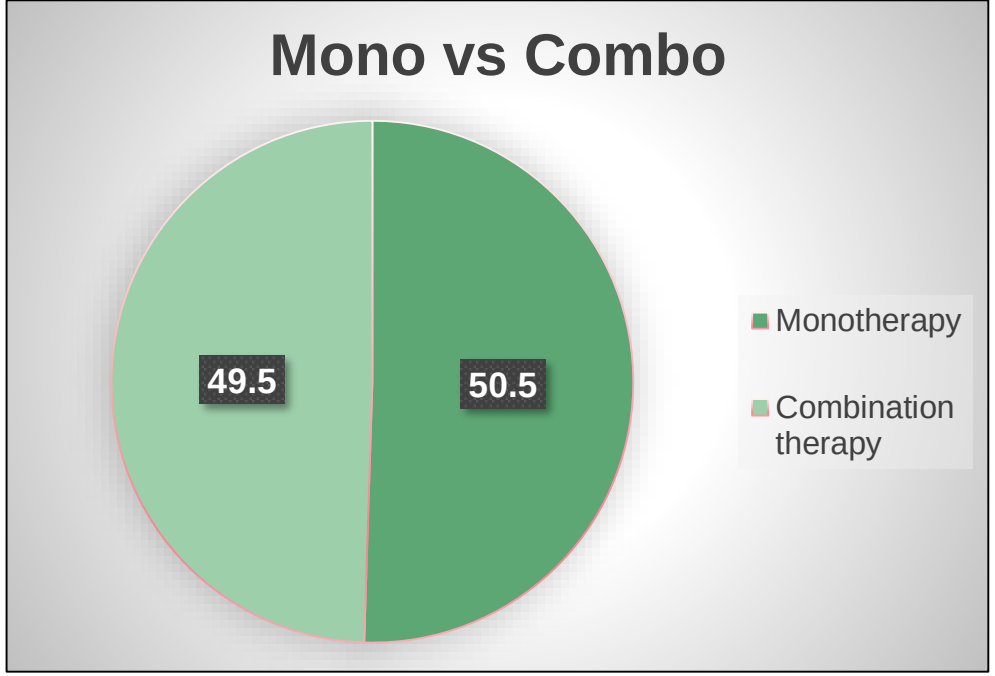
Variables	No. of patients	%	95% CI
Variables at cefiderocol initiation			
Days from admission to cefiderocol initiation, median (IQR)	22 (10–40)	–	9–25
ICU stay	102/200	51.0	44.0–58.0
SOFA score, median (IQR)	5 (3–7)	–	2–5
Presence of CVC	140/194	72.2	65.5–78.2
Presence of urinary catheter	155/195	79.5	73.2–84.8
Presence of septic shock	51/198	25.8	20.0–32.2
Presence of ARDS	21/192	10.9	7.1–16.0
Presence of AKI	68/199	34.2	27.8–41.2
Concomitant COVID-19	16/197	8.1	4.9–12.8
Total parenteral nutrition	55/191	28.8	22.7–35.5
Neutropenia	10/200	5.0	2.6–8.8
CRRT	26/198	13.1	8.9–18.5
ECMO	5/198	2.5	1.0–5.6
White blood cell × 10^{-3}/mm^3, median (IQR)	10.26 (5.58–15.34)	–	4.9–12.0
Serum C-reactive protein in mg/L, median (IQR)	84.3 (22.8–154.0)	–	69–104
Serum procalcitonin in ng/mL, median (IQR)	1.4 (0.3–5.1)	–	0.9–1.9

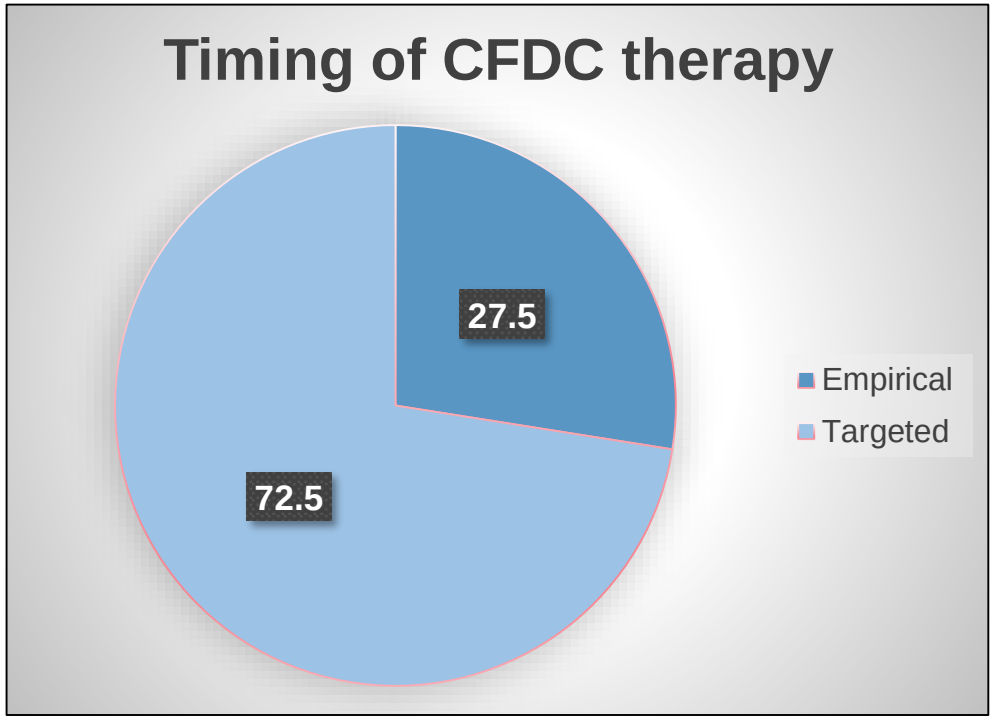
ICU stay	**51,0%**
CVC	**72,2%**
Septic shock	**25,8%**
AKI	**34,2%**
CRRT	**13,1%**
ECMO	**2,5%**

Mono/Combo, Empirical/Targeted

Table 2 Characteristics of cefiderocol therapy

Variables[a]	No. of patients	%	95% CI
Type of anti-CR-GNB therapy[b]			
Cefiderocol monotherapy	101/200	50.5	43.5–57.5
Combination therapy[c,d,e,f,g]	99/200	49.5	42.5–56.5
Timing of cefiderocol therapy			
Empirical therapy[h]	55/200	27.5	21.6–34.2
Empirical cefiderocol monotherapy	23/55	41.8	28.7–55.5
Empirical combination therapy	32/55	58.2	44.5–71.3
Targeted therapy[I]	145/200	72.5	65.8–78.4
Targeted cefiderocol monotherapy	69/145	47.6	39.2–55.9
Targeted combination therapy	76/145	52.4	44.1–60.8





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RESEARCH ARTICLE

In Vitro Activities and Inoculum Effects of Cefiderocol and Aztreonam-Avibactam against Metallo-β-Lactamase-Producing *Enterobacteriaceae*

Yu-Shan Huang,[a,b] Pao-Yu Chen,[a,b] Pei-Chun Chou,[c] Jann-Tay Wang[a]

- **The inoculum effect** of cefiderocol and ATM-AVI were observed in 98.4% (121/123) and 94.2% (129/137) of MBL CPE isolates, respectively.

- Compared to MBL CPE, **KPC CPE** showed a significantly **lower rate of** inoculum effect for **cefiderocol** (98.4% [121/123] versus 88.6% [31/35], P = 0.022).

- The frequency of inoculum effect for cefiderocol or ATM-AVI were **comparable** among **NDM, IMP, and VIM** CPE.

Type of combo therapy

Empirical	Targeted Enterobacterales	Targeted Pseudomonas	Targeted AciBau	Targeted Steno
Fosfomycin	Fosfomycin	Fosfomycin	Amp/Sul	Colistin+Tigecycline
Tigecycline	Tigecycline	Aminoglycoside	Colistin	
Colistin	Aminoglycoside	Colistin	Tigecycline	
Colistin+Tigecycline	Aminoglycoside+ tigecycline		Aminoglycoside	
Aminoglycoside			Aminoglycoside+ tigecycline	
Aminoglycoside+ fosfomycine			Amp/Sul+Tigecycline	
Amp/Sul+Tigecycline			Colistin+Tigecycline	

antibiotics

MDPI

Article

Synergistic Activity of Cefiderocol in Combination with Piperacillin-Tazobactam, Fosfomycin, Ampicillin-Sulbactam, Imipenem-Relebactam and Ceftazidime-Avibactam against Carbapenem-Resistant Gram-Negative Bacteria

Marta Palombo [1], Federica Bovo [2], Stefano Amadesi [1] and Paolo Gaibani [1,*]

Isolates	MIC (mg/L) [1]							
	CFD [2]	SULB [3]	PIP-TAZ [4]	IMI-REL [5]	MER-VAB [6]	CAZ-AVI [7]	AMP-SULB [8]	FOS [9]
CRE 1	**16**	**>256**	**>256** [a]	**4** [b]	**16** [c]	**48** [d]	**>256** [e]	**>256**
CRE 2	0.032	**>256**	**>256** [a]	0.25 [b]	4 [c]	3 [d]	**>256** [e]	8
CR-Ab 1	**>256**	**>256**	**>256** [a]	**>32** [b]	**>256** [c]	**>256** [d]	**>256** [e]	32
CR-Ab 2	0.125	**64**	**>256** [a]	**>32** [b]	**>256** [c]	**48** [d]	**>256** [e]	**>256**
CR-Pa 1	0.5	**>256**	**12** [a]	2 [b]	**16** [c]	**24** [d]	**>256** [e]	**>256**
CR-Pa 2	0.125	**>256**	8 [a]	**>32** [b]	**32** [c]	8 [d]	**>256** [e]	**>256**

are reported in bold.

Isolates	CFD/PIP-TAZ [1]	CFD/FOS [2]	CFD/CAZ-AVI [3]	CFD/IMI-REL [4]	CFD/MER-VAB [5]	CFD/AMP-SULB [6]
CRE 1	1.25	**0.50**	**0.38**	0.63	0.63	0.88
CRE 2	1.00	0.86	0.83	1.00	0.75	1.47
CR-Ab 1	2.00	**0.44**	2.00	2.00	2.00	2.00
CR-Ab 2	1.50	1.01	1.75	2.00	2.00	1.50
CR-Pa 1	1.00	1.00	**0.50**	0.63	1.25	**0.50**
CR-Pa 2	2	1.75	2	0.63	1.26	2

Empirical therapy – Indication

Supplementary table S1. Infections treated with empirical and targeted cefiderocol

Variables [a]	No. of patients	%	95% CI
Reported indication for empirical therapy			
Sepsis	36/55	65.5	51.8-77.8
Lower respiratory tract infection	10/55	18.2	9.4-30.6
Intra-abdominal infection	6/55	10.9	4.9-22.2
Surgical site infection	2/55	3.6	0.7-12.1
Other indication (not further specified)	1/55	1.8	0.1-9.3

- **55 patients**
- **Most frequently reported indication for empirical therapy was sepsis (65%) and LRTI (18,2%)**

Il rischio più elevato di infezione si osserva in pazienti colonizzati da batteri Gram-negativi resistenti ai carbapenemi

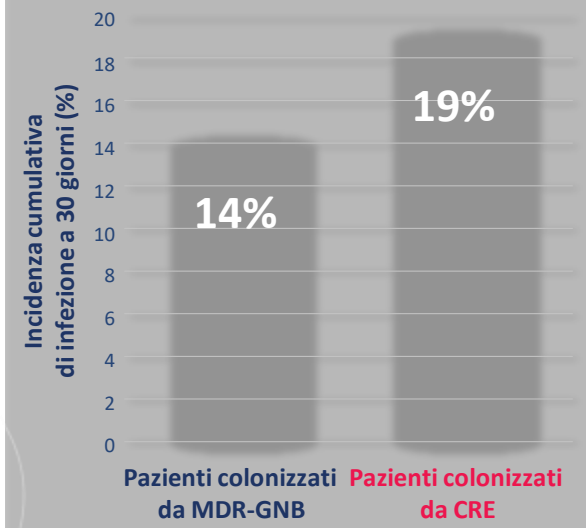
Rischio di sviluppo di infezione in pazienti colonizzati da *P. aeruginosa*[2]

- Nei pazienti colonizzati da ***P. aeruginosa***
  la probabilità di una coltura successiva positiva è stata più elevata rispetto ai pazienti non colonizzati (**IRR 6,74**; IC 95% 4,91-9,25)[2]

Rischio di infezione in pazienti colonizzati da *A. baumannii* CR[3]

- *Il **23% dei pazienti colonizzati** da CR (26/115) **ha sviluppato un'infezione** clinica rispetto al **14% dei non colonizzati** (23/166, p=0,05)*[3]

Rischio globale di infezione in pazienti colonizzati da CRE[1]



Elaborazione grafica da testo, rif. 1.

CR: resistente ai carbapenemi. **CRE**: *Enterobacterales* resistenti ai carbapenemi. **IC**: intervallo di confidenza. **IRR**: incidence rate ratio. **MDR-GBN**: batteri Gram-negativi multiresistenti.

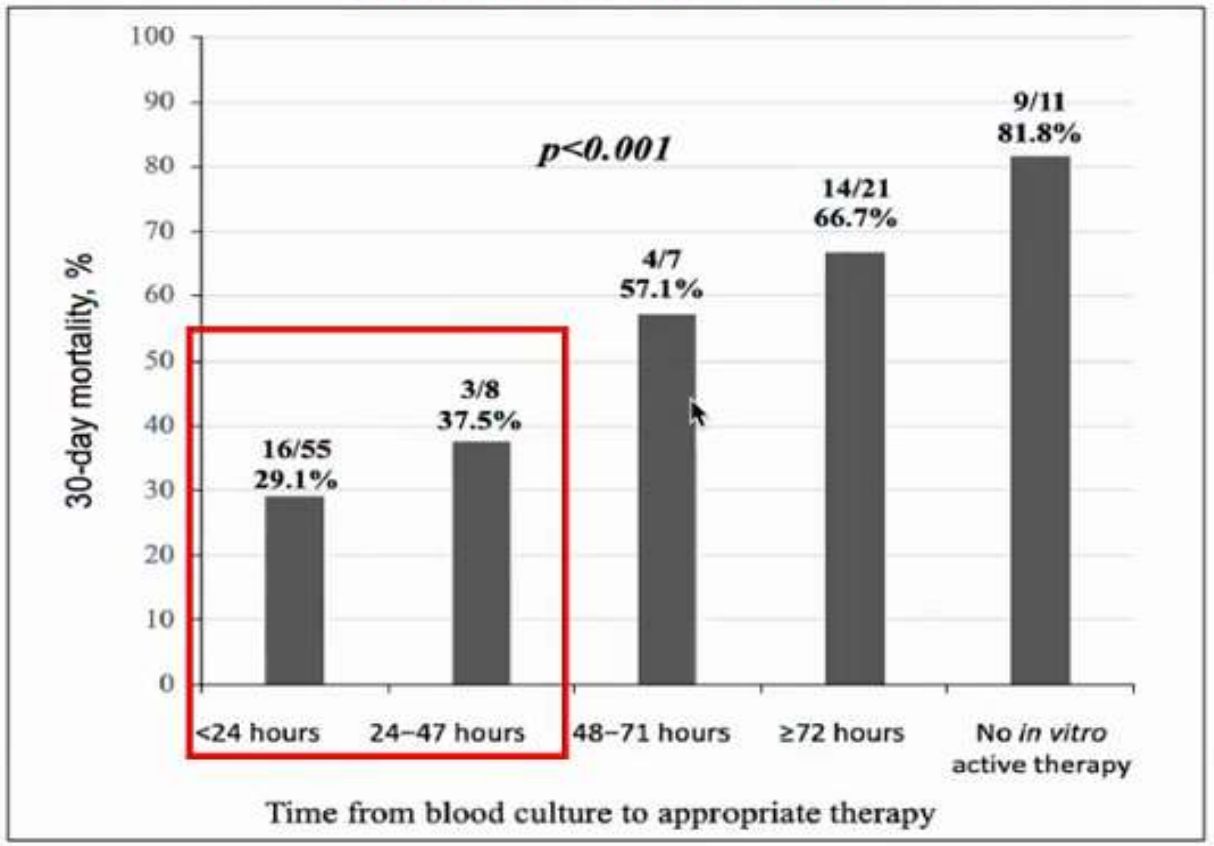
1. Willems RPJ, et al. Lancet Infect Dis. 2023;23(6):719-731. **2.** Harris AD, et al. Infect Control Hosp Epidemiol. 2016;37(5):544-8. **3.** Wiener-Well Y, et al. Isr Med Assoc J. 2022;24(4):235-240.

Time to appropriate antibiotic therapy is a predictor of outcome in patients with BSI caused by KPC-producing *Klebsiella pneumoniae*

- 102 consecutive patients with KPC-Kp bacteraemia hospitalised in the ICU
- Two tertiary care hospitals
  - Pisa
  - Udine

BSI, bloodstream infection; ICU, intensive care unit; KPC-Kp, *Klebsiella pneumoniae* carbapenemase-producing *Klebsiella pneumoniae*.

Thirty-day mortality rates by time from blood culture collection to appropriate antibiotic therapy



Falcone M, et al. *Critical Care* 2020; 24:29

Summary of Shorter is Better RCTs

Davas K et al OFID 2023

Diagnosis	Short (d)	Long (d)	Result	No. of RCTs	Refs.
Community-acquired pneumonia	3–5	5–14	Equal	14	[32–45]
Atypical community-acquired pneumonia	1	3	Equal	1	[46]
Possible pneumonia in ICU	3	14–21	Equal	1	[47]
Ventilator-associated pneumonia	8	15	Equal	2	[48, 49]
Complicated UTI/pyelonephritis	5 or 7	10 or 14	Equal	9	[50–58]
Complicated intra-abdominal infection	4–8	10–15	Equal	2	[59, 60]
Gram-negative bacillus bacteremia	7	14	Equal	3	[61–63]
Cellulitis/wound/abscess	5–6	10	Equal	4	[64–67]
Osteomyelitis	42	84	Equal	2	[68, 69]
Osteomyelitis s/*P* implant removal	28	42	Equal	1	[70]
Diabetic osteomyelitis s/*P* Debridement	10–21	42–90	Equal	2	[71, 72]
Septic arthritis	14	28	Equal	1	[73]
Acute exacerbations of bronchitis and sinusitis	≤5	≥7	Equal	>25	[74–81]
Neutropenic fever	AFx72 h/3d	ANC > 500/9d	Equal	2	[82, 83]
Perioperative prophylaxis	0–1	1–5	Equal	56	[84–88]
Plasmodium vivax malaria	7	14	Equal	1	[89]
Erythema migrans (Lyme disease)	7	14	Equal	1	[90]

Abbreviations: ANC, absolute neutrophil count; d, day; h, hour; ICU, intensive care unit; RCT, randomized controlled trial; Refs., references; UTI, urinary tract infection.

Effective Durations of Therapy for CRE Bloodstream Infections: A Multicenter Observational Study

Soto CL et al. Clin Infect Dis 2023 Aug 16

- **183 adults with CRE-BSI, 24 US hospitals**
  - **Short-courses of active therapy**
    - 7-10 days, median 9 days
  - **Prolonged courses of active therapy**
    - 14-21 days, median 14 days
- **Similar odds, propensity-score-weighted analysis**
  - **Recurrent bacteremia or death within 30 days**

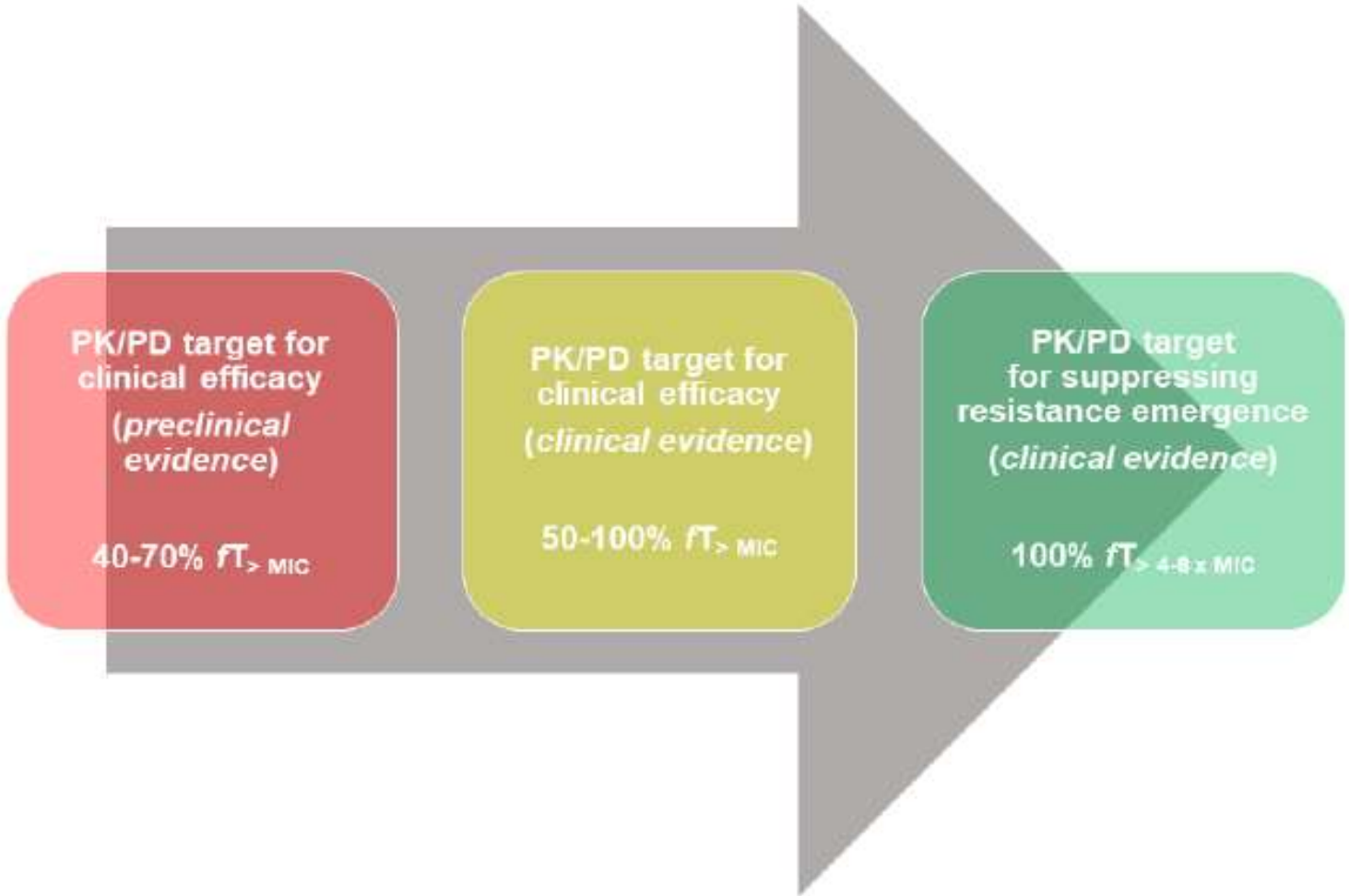
Future of ID & Inertial Dogmas (1)

Davas K et al OFID 2023

- **Many dogmas underpin much clinical practice**
  - Mainly based on uncontrolled case series
    - From >50 years ago
  - Amplified by the opinions of eminent experts
    - "A-old" amplified by "C-III"

- **Specific dogmas to be discussed:**
  - Traditional durations of antimicrobial therapy
  - Necessity of intravenous (IV)-only therapy
    - For specific infectious syndromes
- **TDM needs to be implemented**
  - Precise MICs...

A PARADIGM SHIFT IN THE IMPLEMENTATION OF A TDM-GUIDED STRATEGY IN THE MANAGEMENT OF GRAM-NEGATIVE INFECTIONS



UNIVERSITY

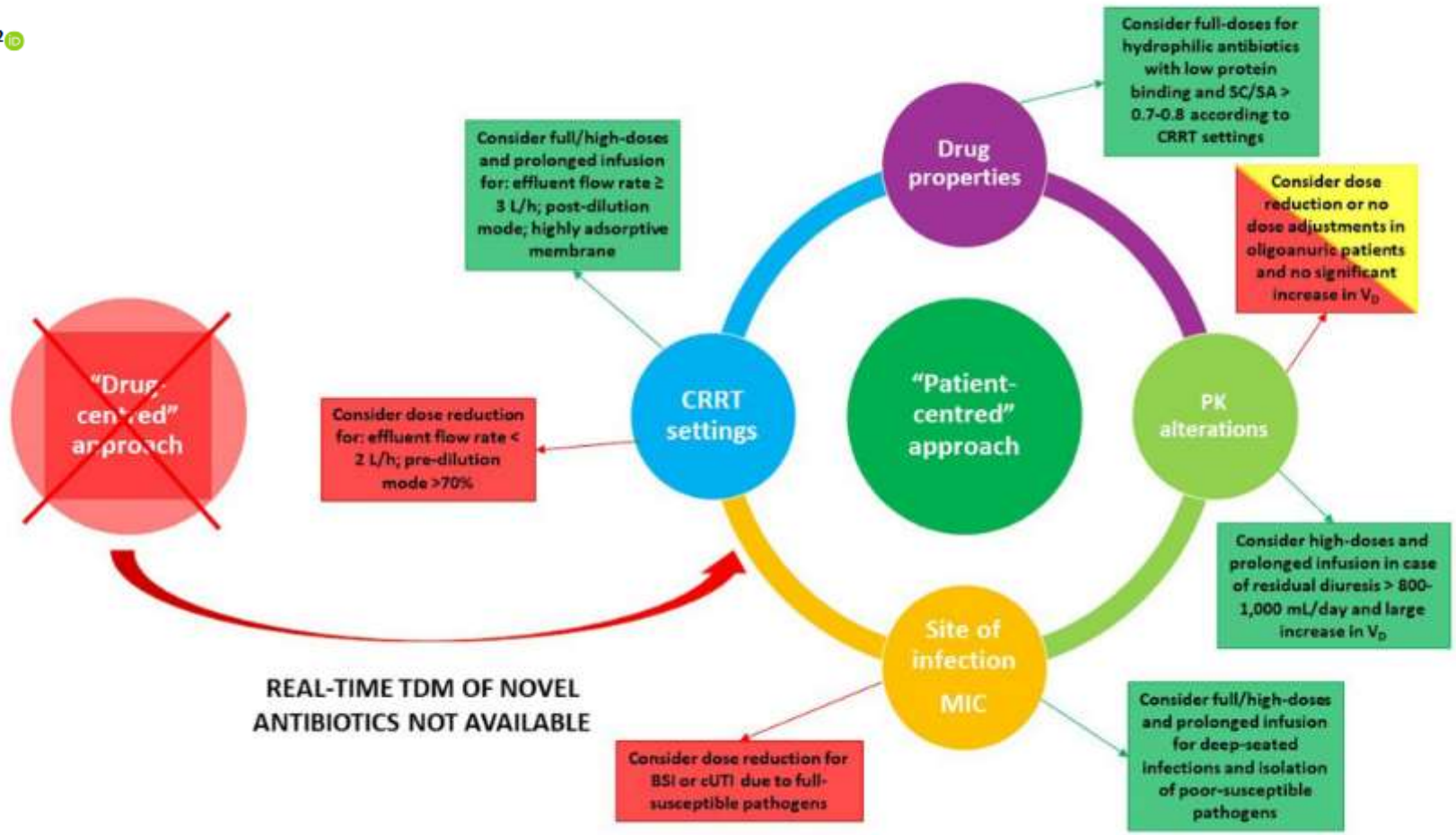
Courtesy of Dr Gatti M.

Clinical Pharmacokinetics (2021) 60:1271–1289
https://doi.org/10.1007/s40262-021-01040-y

REVIEW ARTICLE

Antimicrobial Dose Reduction in Continuous Renal Replacement Therapy: Myth or Real Need? A Practical Approach for Guiding Dose Optimization of Novel Antibiotics

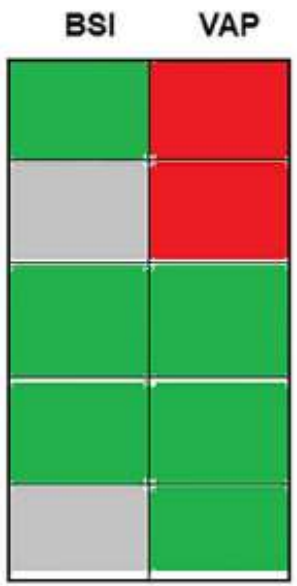
Milo Gatti[1,2] · Federico Pea[1,2]



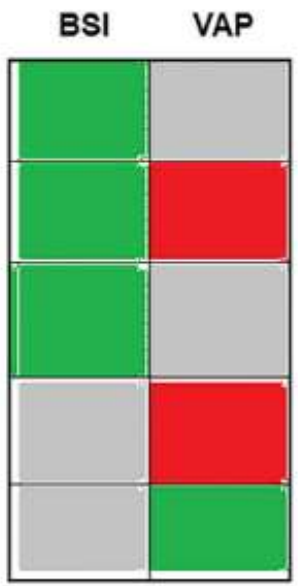
ID	Age/sex	BMI (kg/m^2)	Type of infection (bacterial load in BAL)	Cefiderocol MIC (mg/L)	Cefiderocol dosage (infused over 3 h)	fC_{min}/MIC [a]	Antibiotic co-treatment	CRRT/ECMO	ME BSI	ME VAP	30-day mortality
#1	55/F	27.1	BSI + VAP (>10^6)	0.5	1.5 g q8h	26.71	No	ECMO	Yes	No (>10^6)	No
#2	57/M	24.5	BSI	0.5	2 g q8h	3.11	No	ECMO	Yes	NA	Yes
#3	15/M	27.8	VAP (>10^6)	1	2 g q8h	6.89	No		NA	No (>10^6)	No
#4	75/F	32.7	BSI + VAP (>10^6)	0.5	2 g q8h	5.38		ECMO + CVVHDF CVVHDF	Yes	Yes	Yes
#5	54/M	31.6	BSI + VAP (>10^5)	1	2 g q8h	0.59	Colistin + SAM Fosfomycin	No	No	No (>10^6)	No
#6	67/F	31.3	BSI + VAP (10^6)	1	2 g q8h	2.94	No	No	Yes	No (10^6)	No
#7	65/M	29.4	BSI	0.5	2 g q8h	1.09	SAM	No	Yes	NA	Yes
#8	49/M	37.6	VAP (>10^6)	1	2 g q8h	2.39	No	ECMO	NA	No (>10^5)	No
#9	76/M	29.4	VAP (10^4)	1	2 g q8h	0.67	No	No	NA	No (>10^6)	No
#10	77/M	23.0	VAP (>10^6)	1	1.5 g q8h	2.35	No	No	NA	Yes	No
#11	68/F	27.1	BSI + VAP (10^5)	1	2 g q8h	0.63	No	No	Yes	No (10^5)	No
#12	72/F	56.9	BSI + VAP (10^6)	0.5	2 g q8h	28.39	No	No	Yes	Yes	No
#13	78/M	27.8	VAP (10^5)	1	2 g q8h	6.47	No	No	NA	Yes	Yes

BAL, bronchoalveolar lavage; BMI, body mass index; BSI, bloodstream infection; C_{min}, trough concentration; CRRT, continuous renal replacement therapy; CVVHDF, continuous venovenous haemodiafiltration; ECMO, extracorporeal membrane oxygenation; fC_{min}, plasma cefiderocol trough concentration of the free fraction; ME, microbiological eradication; MIC, minimum inhibitory concentration; NA, not applicable; q8, every 8 h; SAM, ampicillin/sulbactam; VAP, ventilator-associated pneumonia.

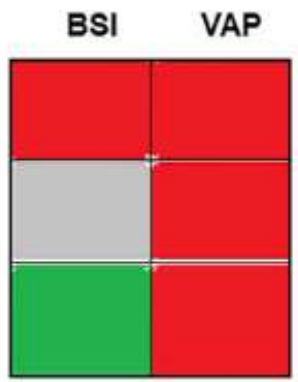
[a] Estimated considering plasma protein binding of 58% [2].



Optimal fC_{min}/MIC ratio



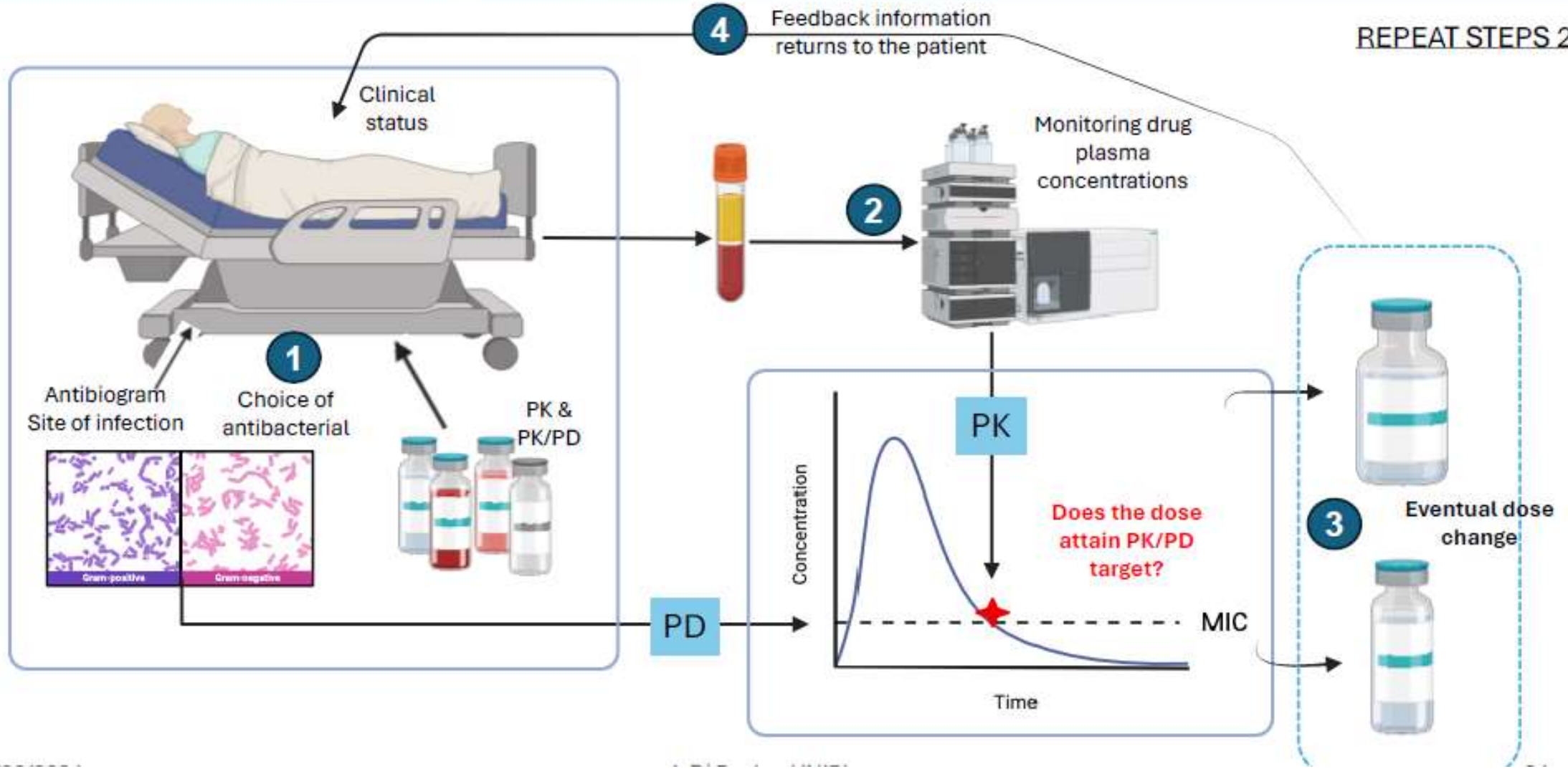
Quasi-optimal fC_{min}/MIC ratio



Sub-optimal fC_{min}/MIC ratio

Gatti, J Gl0bal Resist 2021

I servizi integrati di TDM: MIPD



Progetto TDM Torino (implementazione 2026)

Reparti selezionati nell'ambito di **ASL Città di Torino, Osp. San Luigi, IRCCS Candiolo, ASL TO 4, ASL TO5**

Target di **pazienti e farmaci selezionati** da medici curanti + consulenti infettivologi

Dosaggio farmaci con **turnaround time per refertazioe di 6-8 ore**

Lab di Farmacologia e Farmacogenetica Ospedale Amedeo di Savoia (Prof. D'Avolio)

Valutazione comparata dosaggio e dati clinici del paziente da parte della Farmacologia Clinica di Bologna (dott. Gatti) **e produzione di referto in 4-6 ore**

Microbiologia di riferimento

Grazie