28° Meeting GiViTI

13-14-15 Novembre 2019
Hotel Baia Flaminia, Pesaro

Bruno Viaggi
Dipartimento di Anestesia
SOD NeuroAnestesia e
Rianimazione CTO AOUC

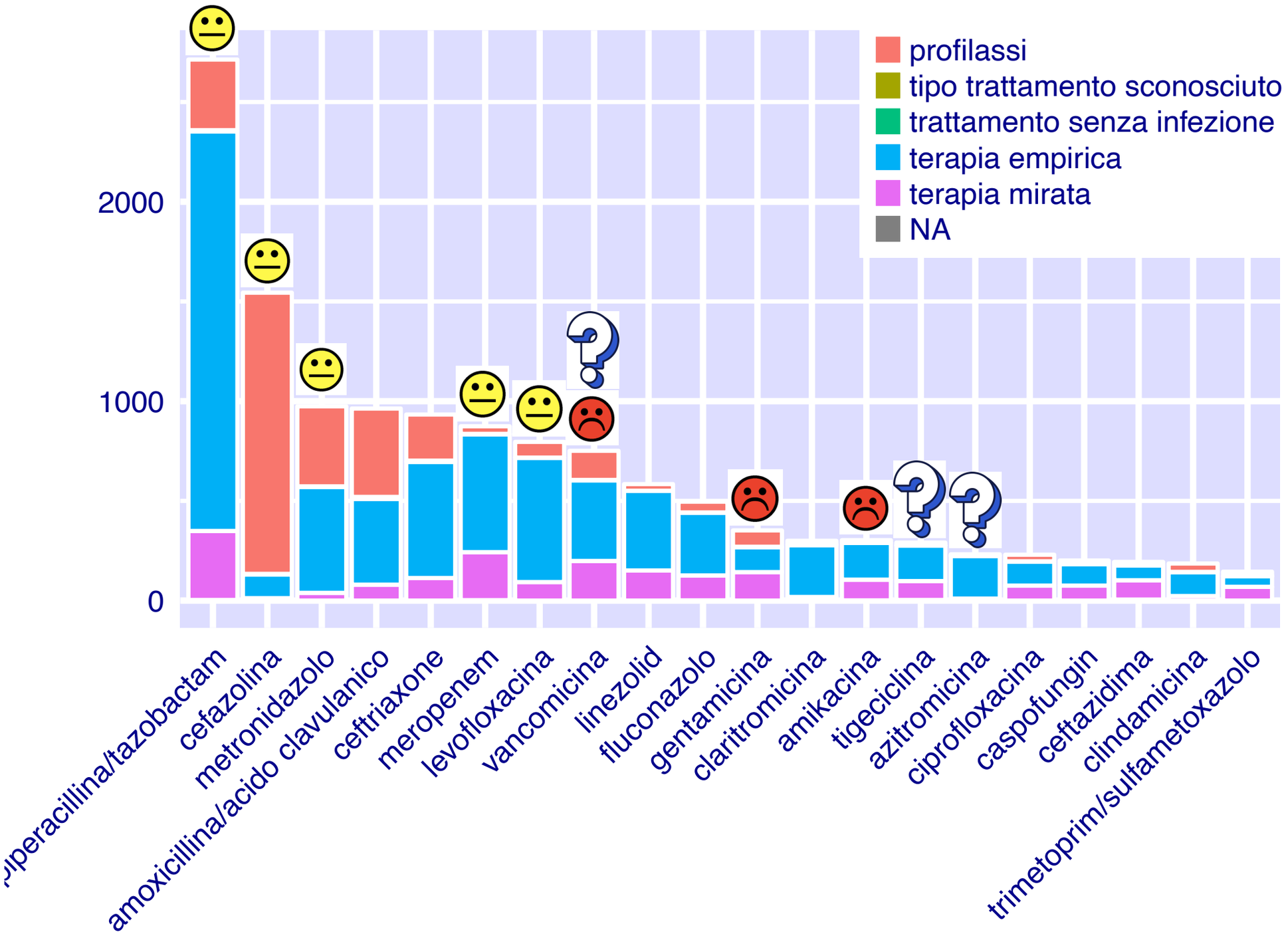
Dichiarazione su potenziali conflitti di interesse
Consulenze, partecipazione advisory boards, speaker's bureau, contratti/contributi di ricerca e di eventi studio:
Abbott**, **Accelerate Diagnostics, Ada, Alifax, Angelini, Becton Dickinson, Bellco, Biomerieux, Biotest, Cepheid, MSD Italia, Nordic Pharma, Pfizer, Thermofischer Scientific

Giulia Mandelli
Centro di Coordinamento GiViTi
IRCCS - Istituto di Ricerche
Farmacologiche Mario Negri

Uso e consumo degli antibiotici, quali novità in 5 anni?

Molecole più utilizzate

2019 vs **2014**



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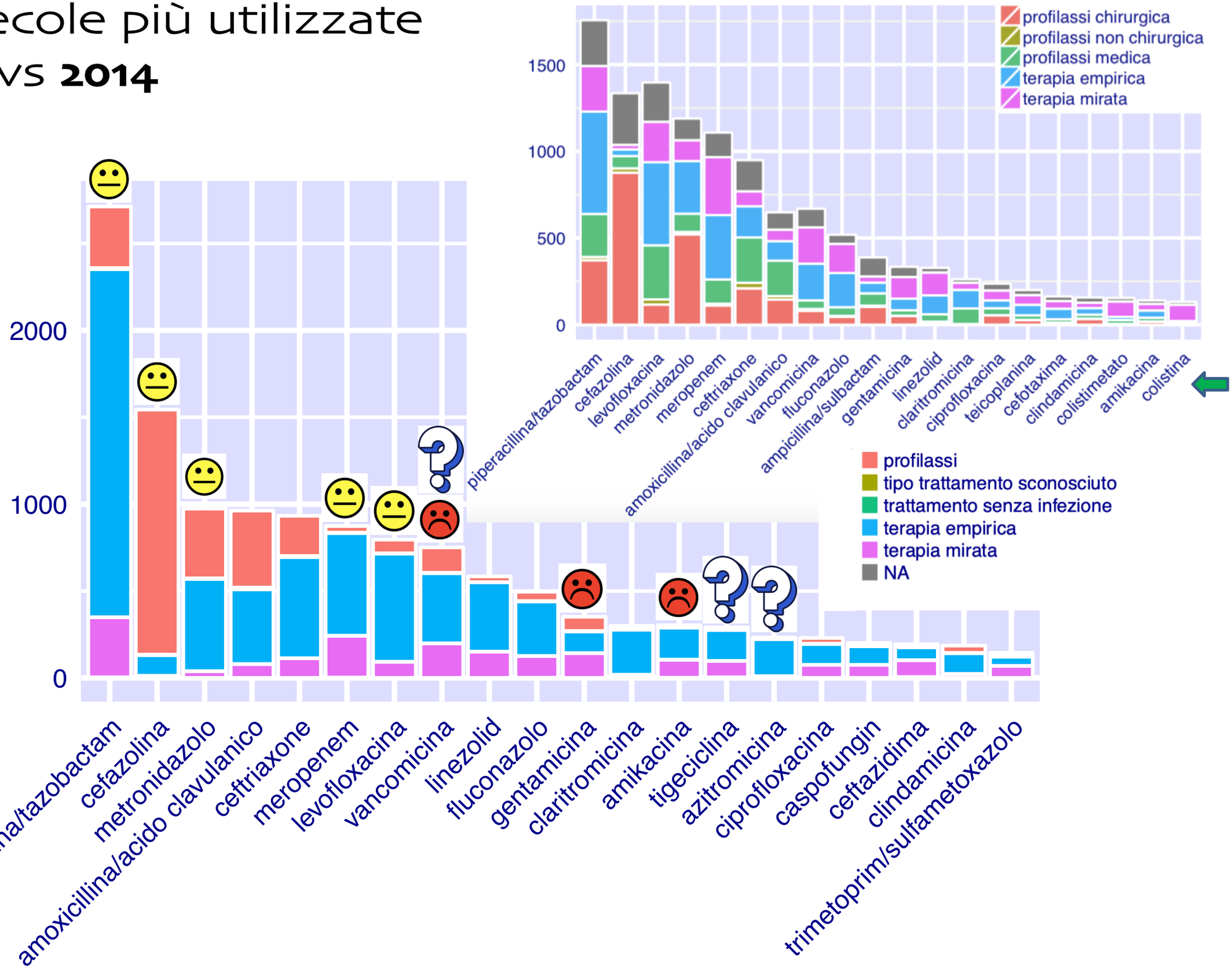


In vivo evolution of resistance of Pseudomonas aeruginosa strains isolated from patients admitted to an ICU: mechanisms of resistance and antimicrobial exposure

Mar Sole et al J Antimicrob Chemother 2015

piperacillin/tazobactam combination *has the lowest potential for selecting overproducing efflux pump and AmpC derepressed mutants*

Taking into account that no strain was resistant to ***amikacin****, the use of piperacillin/tazobactam and/or amikacin seems to be appropriate for treating these complicated infections in this particular patient population.*

Does ARC have a negative impact on continuously infused TZP concentrations?

Carrié C et al J Crit Care Dec 2018

59 *critically ill ptz .. no IRC .. Cr_{CL}24h + TDM 24h 48h 72h*
Underexposure *defined by at least one of 3 samples < 16 mg/L*
Monte Carlo simulation
RESULTS: ***19%*** *one o more C < 100%$fT_{>MIC}$ significantly higher in* ***ARC*** *patients (0 vs. 31%, p = 0.003)*

Antimicrobial treatment challenges in the era of carbapenem resistance

Peri AN et al Diagn Microbiol Infect Dis 2019

Among other molecules, aminoglycosides are also active against ESBL and may be useful in cUTI and sepsis, although concerns regarding toxicity and limitation in PK/PD target attainment have been reported. In areas with high ESBL prevalence, ***addition of an aminoglycoside to piperacillin-tazobactam could be useful for empiric therapy***

… in a carbapenem-sparing regimen

In ARC patients, a 20g/2.5g/24hr PTZ dosing regimen was associated with the highest probability to reach the 16 mg/L empirical target, without risk of excessive dosing

And LD?

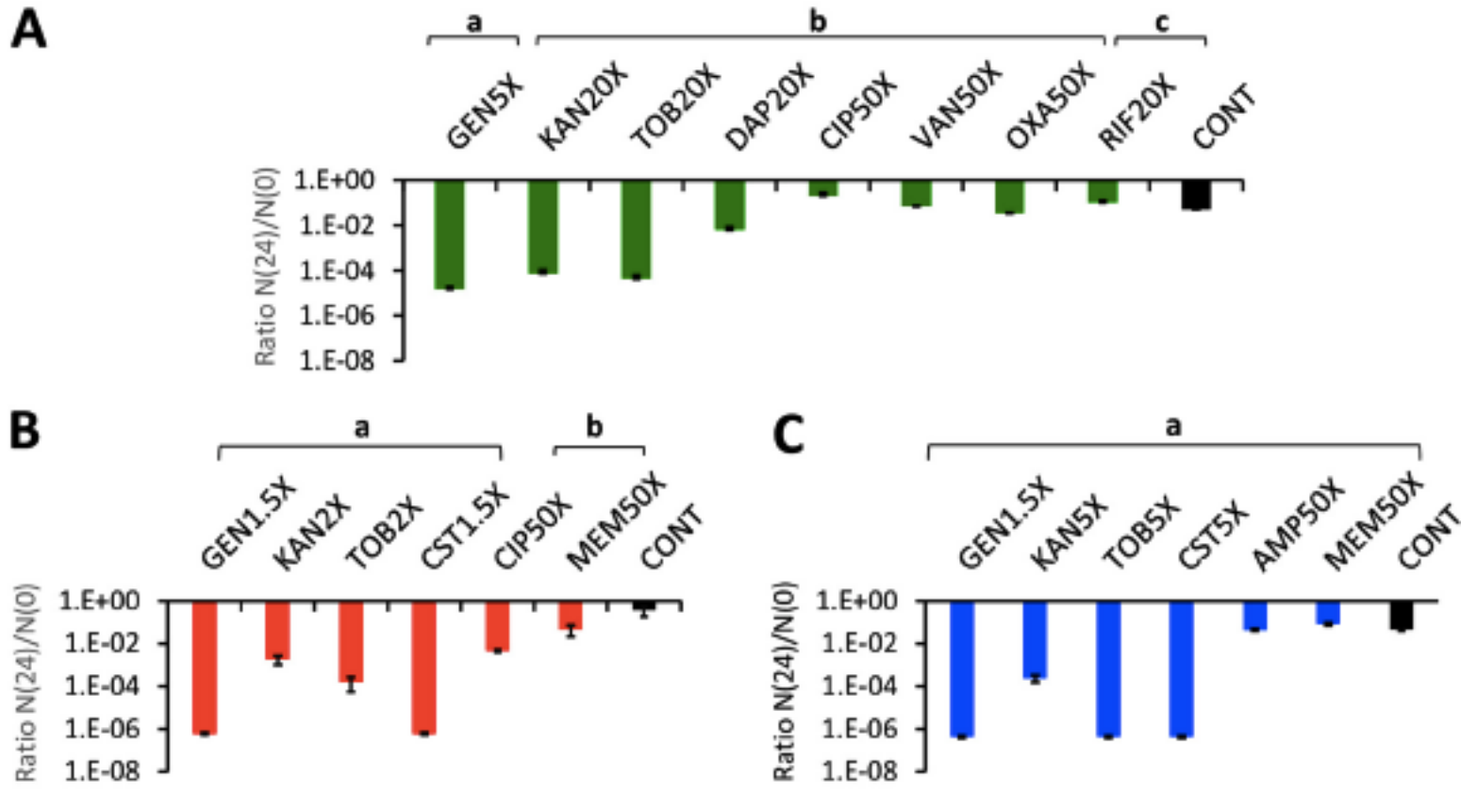
Antibiotic Killing of Diversely Generated Populations of Nonreplicating Bacteria

McCall IC et al F Antimicrob Agents Chemother Jul 2019

Nonreplicating bacteria are known to be refractory to antibiotics to which they are genetically susceptible. Here, we explore the sensitivity to killing by bactericidal antibiotics of three classes of nonreplicating populations of planktonic bacteria

- stationary phase
- persisters
- static phase

In contrast to the common belief that bacteria that are non replicating are refractory to antibiotic-mediated killing, all three types of nonreplicating populations of these Gram-positive and Gram-negative bacteria **are consistently killed by aminoglycosides and the peptide antibiotics daptomycin and colistin,** respectively.



Antibiotic-mediated killing of bactericidal persisters.

(A) **S. aureus** treated with 25 MIC ampicillin to generate the persister N(0);

(B) **E. coli** hipA7 treated with 10 MIC ampicillin to generate the persister N(0);

(C) **E. coli** hipA7 mutant treated with 10 MIC ciprofl oxacin to generate the persister N(0).

Antibiotic Killing of Diversely Generated Populations of Nonreplicating Bacteria

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- stationary phase

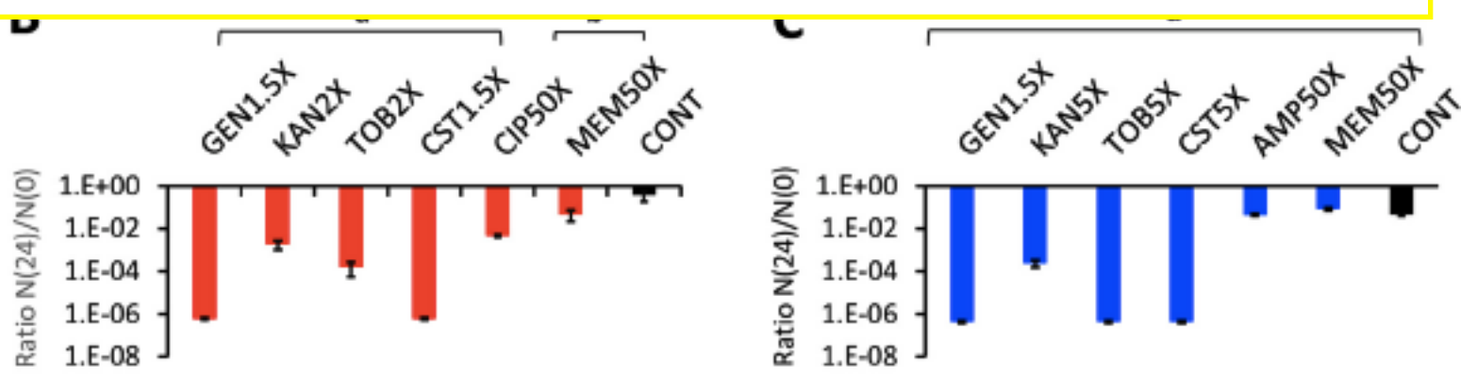
In contrast to the common belief that bacteria that are non replicating are refractory to antibiotic-mediated killing, all three types of nonreplicating populations of these Gram-positive and Gram-negative bacteria **are consistently killed by aminoglycosides**

... the addition of a short-course administration of antibiotics, such as the aminoglycosides and peptides, that kill these nonreplicating bacteria may well accelerate the course of treatment and increase the likelihood of its success ...

(A) **S. aureus** treated with 25 MIC ampicillin to generate the persister N(0);

(B) **E. coli** hipA7 treated with 10 MIC ampicillin to generate the persister N(0);

(C) **E. coli** hipA7 mutant treated with 10 MIC ciprofl oxacin to generate the persister N(0).



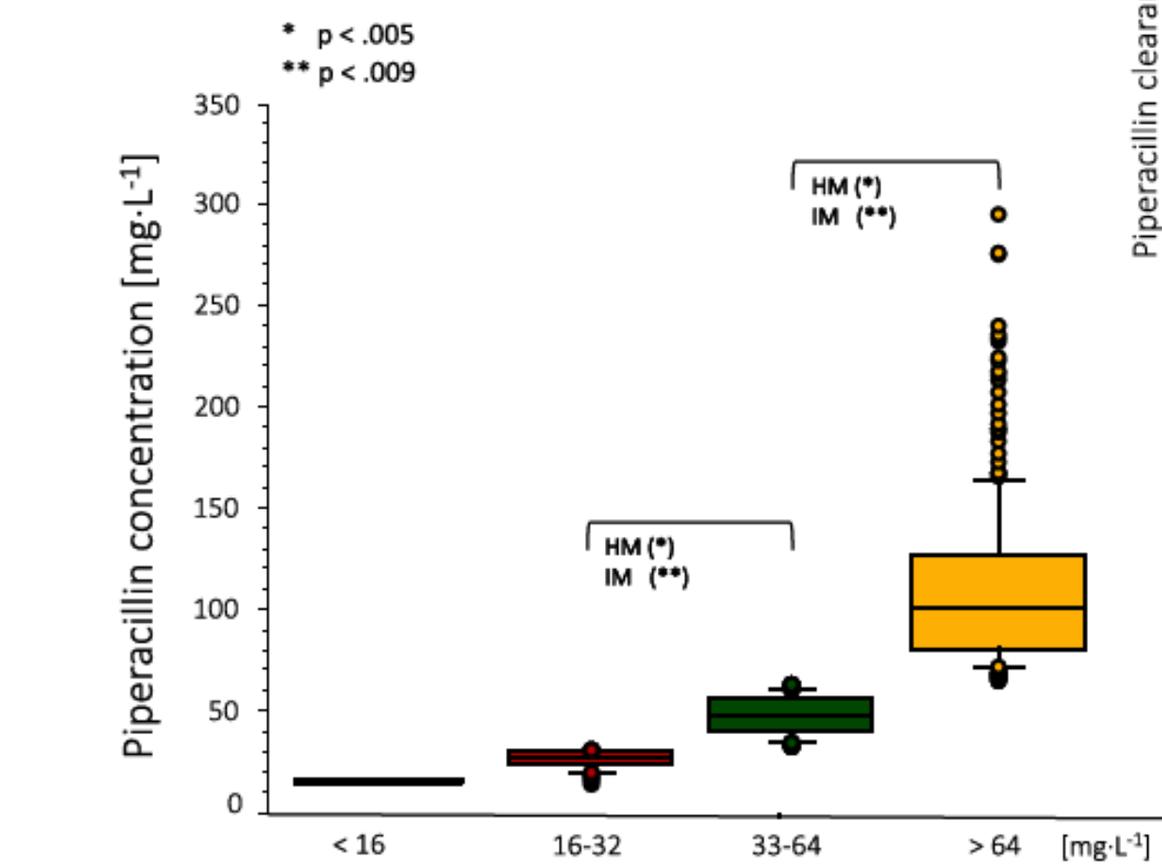
TDM-guided CI of Pip/Taz significantly improves PK target attainment in critically ill patients:

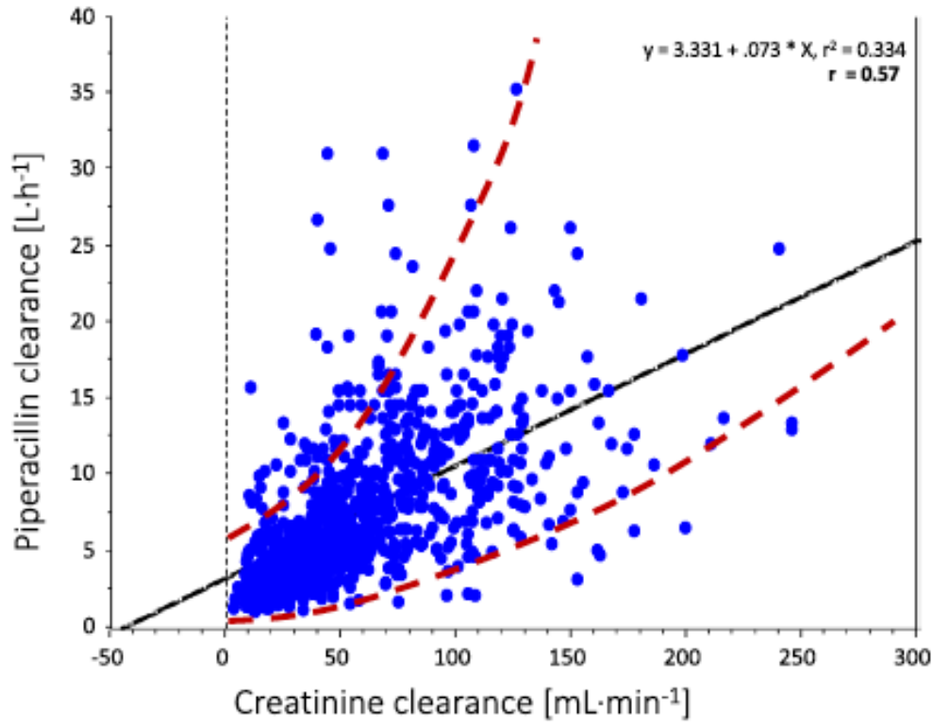
a retrospective analysis of 4 y of clinical experience

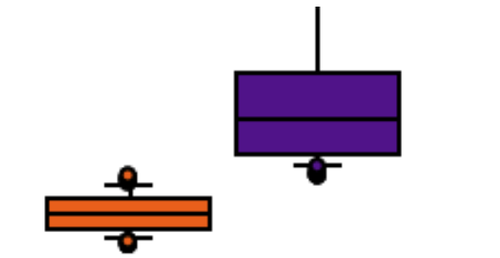
Richter D Infection Aug 2019

We analyzed a PK database of **484** patients with overall years of CI of β-lactams in an ICU

∑ n=484	n=1	n=48	n=166	n=269
	0.2%	9.9%	34.3%	55.6%







Subgroup analysis: n=269 >64 mg·L^{-1}

65-99 ≥100 [mg·L^{-1}]

	< 16	16-32	33-64	> 64	65-99	≥100
ICU mortality (IM) [% (n)]:	14.6 (7)	12.0 (20)	24.5 (66)		16.3 (21)	31.9 (45)
Hospital mortality (HM) [% (n)]:	20.8 (10)	13.9 (23)	29.4 (79)		20.5 (26)	37.6 (53)

TDM-guided CI of Pip/Taz significantly improves PK target attainment in critically ill patients:

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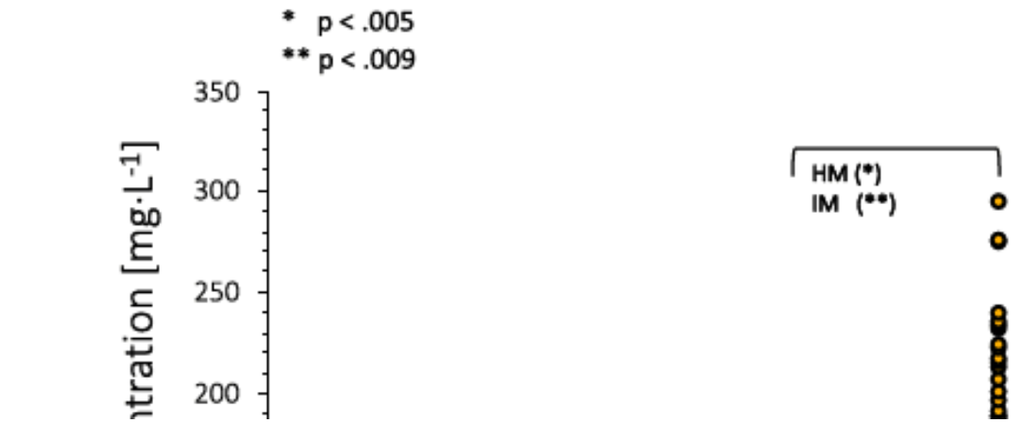
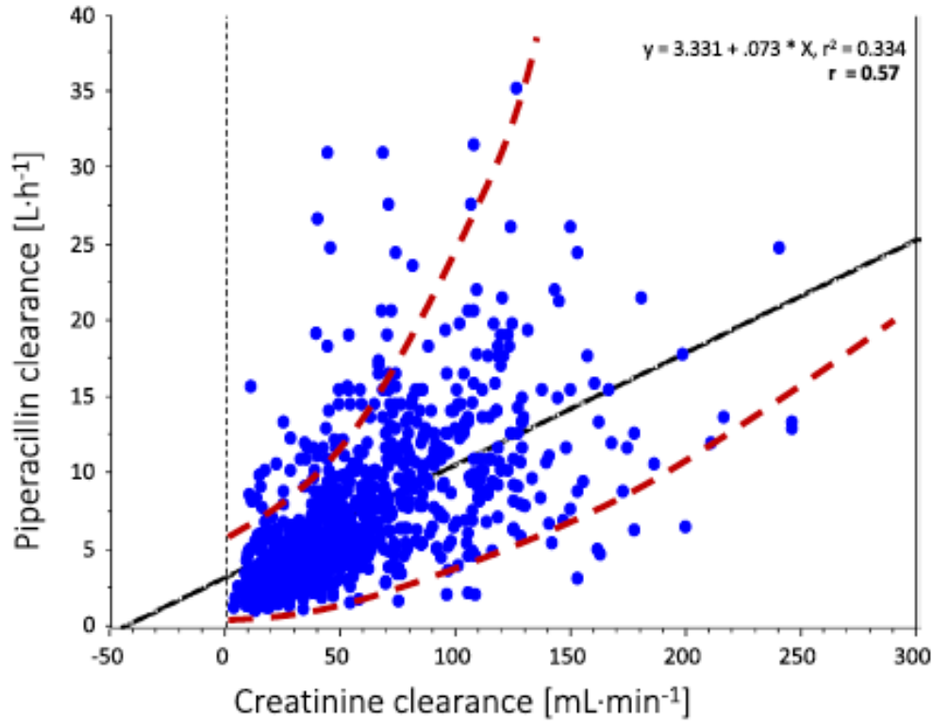
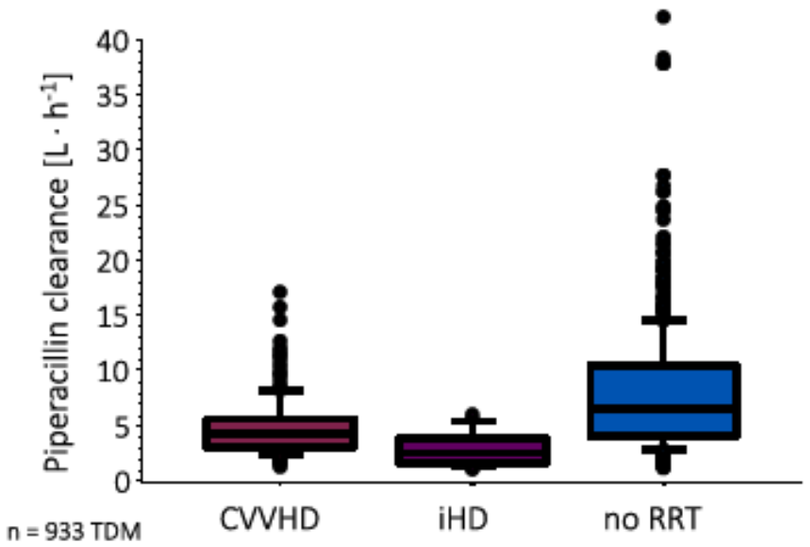




A

n=71	n=8	n=405
14.6%	1.7%	84.1%



B

n=71	n=8	n=405
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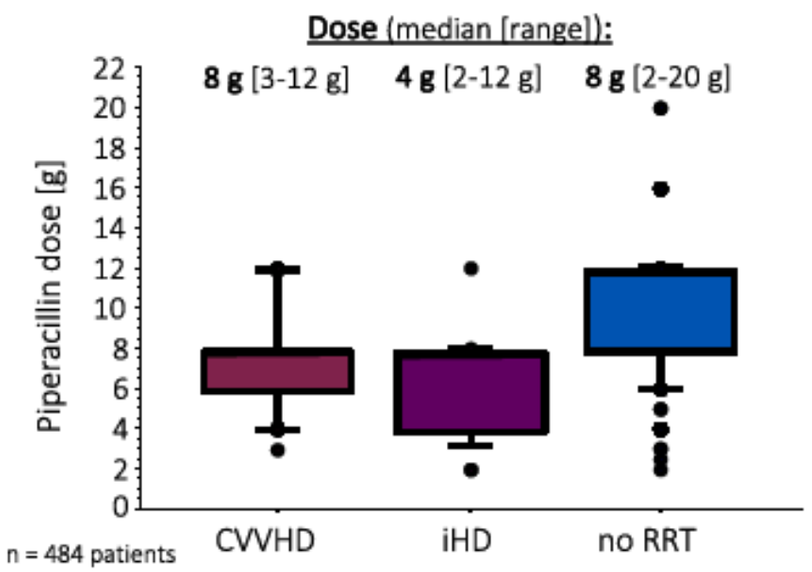


Regardless of the technique used, RRT in general was accompanied by a marked, however not significant, reduction of CLPIP

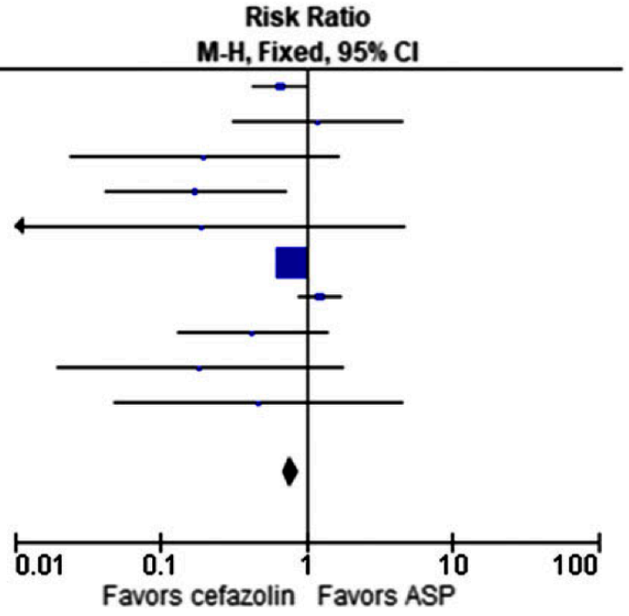
Meta-analysis of trials comparing cefazolin to antistaphylococcal penicillins in the treatment of MSSA bacteraemia

Rindone JP Br J Clin Pharmacol 2018

Nine retrospective and one prospective trials were identified involving 4728 patients, 2954 with ASP and 1774 with cefazolin. Meta-analysis showed ***a lower mortality rate*** *with* ***cefazolin*** *vs.* ***ASP*** *using fixed effect model [risk ratio (RR) 0.78, 95% confidence interval (CI) 0.69–0.88, P < 0.0001] with borderline high heterogeneity (I2 = 51%).* ***Clinical cure*** *was noted more often with cefazolin (RR 1.09, 95% CI 1.02–1.17, P = 0.02), although no difference was noted with relapse (RR 1.29, 95% CI 0.96–1.74 P = 0.09)*

Study or Subgroup	Cefazolin Events	Total	ASP Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bai *et al.*	21	105	75	249	9.1%	0.66 [0.43, 1.02]
Flynt *et al.*	4	68	4	81	0.7%	1.19 [0.31, 4.59]
Lee *et al.* 1	1	41	5	41	1.0%	0.20 [0.02, 1.64]
Lee *et al.* 2	2	79	24	163	3.2%	0.17 [0.04, 0.71]
Li *et al.*	0	59	1	34	0.4%	0.19 [0.01, 4.64]
McDanel *et al.*	231	1163	502	2004	75.3%	0.79 [0.69, 0.91]
Paul *et al.*	29	72	91	281	7.6%	1.24 [0.90, 1.73]
Pollett *et al.*	5	70	5	30	1.4%	0.43 [0.13, 1.37]
Rao *et al.*	1	103	3	58	0.8%	0.19 [0.02, 1.76]
Renaud *et al.*	1	14	2	13	0.4%	0.46 [0.05, 4.53]
Total (95% CI)		**1774**		**2954**	**100.0%**	**0.78 [0.69, 0.88]**
Total events	295		712			

Heterogeneity: Chi² = 18.27, df = 9 (*P* = 0.03); I² = 51%
Test for overall effect: Z = 4.09 (*P* < 0.0001)



CONCLUSION*: Our meta-analysis of retrospective data demonstrate that cefazolin* ***is more effective*** *and* ***safer*** *ASP in patients with MSSA bacteraemia from various causes*

Increased relative abundance of Kbs-pn carbapenemase-producing Kbs-pn within the gut microbiota is associated with risk of bloodstream infection in long-term acute care hospital patients

Shimasaki T et al Clin Infect Dis sept 2018

*2,319 samples from 562 admissions (**506 patients**)*
*255 (**45.4%**) were colonized with KPC-Kp*
*11 (**4.3%**) had KPC-Kp bacteremia*

ROC curve analysis
***relative abundance cutoff of 22%** predicted KPC-Kp bacteremia with sensitivity 73%, specificity 72%, and relative risk 4.2 (P=0.01)*

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CONCLUSIONS: In adult LTACH patients, carbapenem receipt was associated with increased hazard for high relative abundance of KPC-Kp in the gut microbiota.
Increased relative abundance of KPC-Kp was associated with KPC-Kp bacteremia

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 Novembre 2018
EMA/795349/2018

Effetti indesiderati invalidanti e potenzialmente permanenti hanno comportato la sospensione o restrizioni nell' uso di antibiotici chinolonici e fluorochinolonici.

L' EMA ha rivalutato gli effetti indesiderati gravi, invalidanti e potenzialmente permanenti associati all'uso di antibiotici chinolonici e fluorochinolonici somministrati per bocca, iniezione o via inalatoria. La revisione ha incluso i punti di vista dei pazienti, degli operatori sanitari e dell' accademia presentati durante un'audizione pubblica, su fluorochinoloni e chinoloni, organizzata dall'EMA a giugno 2018.

Il Comitato dei Medicinali per Uso Umano dell'EMA (CHMP) ha confermato la raccomandazione del comitato di Valutazione dei Rischi per la Farmacovigilanza (PRAC) e ha concluso che l' autorizzazione all' immissione in commercio dei medicinali contenenti cinoxacina, flumechina, acido nalidissico e acido pipemidico devono essere sospese.

Il CHMP ha concluso che l'uso dei rimanenti antibiotici fluorochinolonici debba essere ristretto. Inoltre, le informazioni del prodotto riservate ad operatori sanitari e le informazioni per i pazienti descriveranno gli effetti indesiderati invalidanti e potenzialmente permanenti e avviseranno i pazienti di interrompere il trattamento con un antibiotico fluorochinolonico al primo segno di un effetto indesiderato che coinvolga il sistema muscolare, i tendini o le articolazioni e il sistema nervoso.

Per restrizioni all'uso di antibiotici fluorochinolonici si intende che essi non devono essere usati:

- per trattare infezioni non gravi o che potrebbero migliorare senza trattamento (come infezioni alla gola);
- per trattare infezioni di origine non batterica, come la prostatite (cronica) non batterica
- per prevenire la diarrea del viaggiatore o le infezioni ricorrenti del tratto urinario inferiore (infezioni delle urine che non si estendono oltre la vescica);
- per il trattamento di infezioni lievi o moderatamente gravi a meno che altri medicinali antibatterici comunemente raccomandati per queste infezioni non possano essere usati.

Soprattutto, i fluorochinoloni devono essere generalmente evitati in pazienti che hanno manifestato precedentemente gravi effetti indesiderati con un antibiotico chinolonico o fluorochinolonico. Devono essere usati con particolare cautela nei pazienti anziani, nei pazienti con problemi renali e nei pazienti che hanno avuto un trapianto di organo perché questi pazienti sono a più alto rischio di danno ai

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

NOTA INFORMATIVA IMPORTANTE CONCORDATA CON LE AUTORITA' REGOLATORIE EUROPEE E L'AGENZIA ITALIANA DEL FARMACO (AIFA)

Aprile 2019

Antibiotici chinolonici e fluorochinolonici per uso sistemico e inalatorio

Rischio di effetti indesiderati invalidanti, di lunga durata e potenzialmente permanenti e restrizioni d'uso

Gentile Dottoressa/Egregio Dottore,

i titolari dell'Autorizzazione all'Immissione in Commercio degli antibiotici chinolonici e fluorochinolonici, in collaborazione con l'Agenzia Europea dei Medicinali (EMA) e l'Agenzia Italiana del Farmaco (AIFA), desiderano informarla di quanto segue:

Riassunto

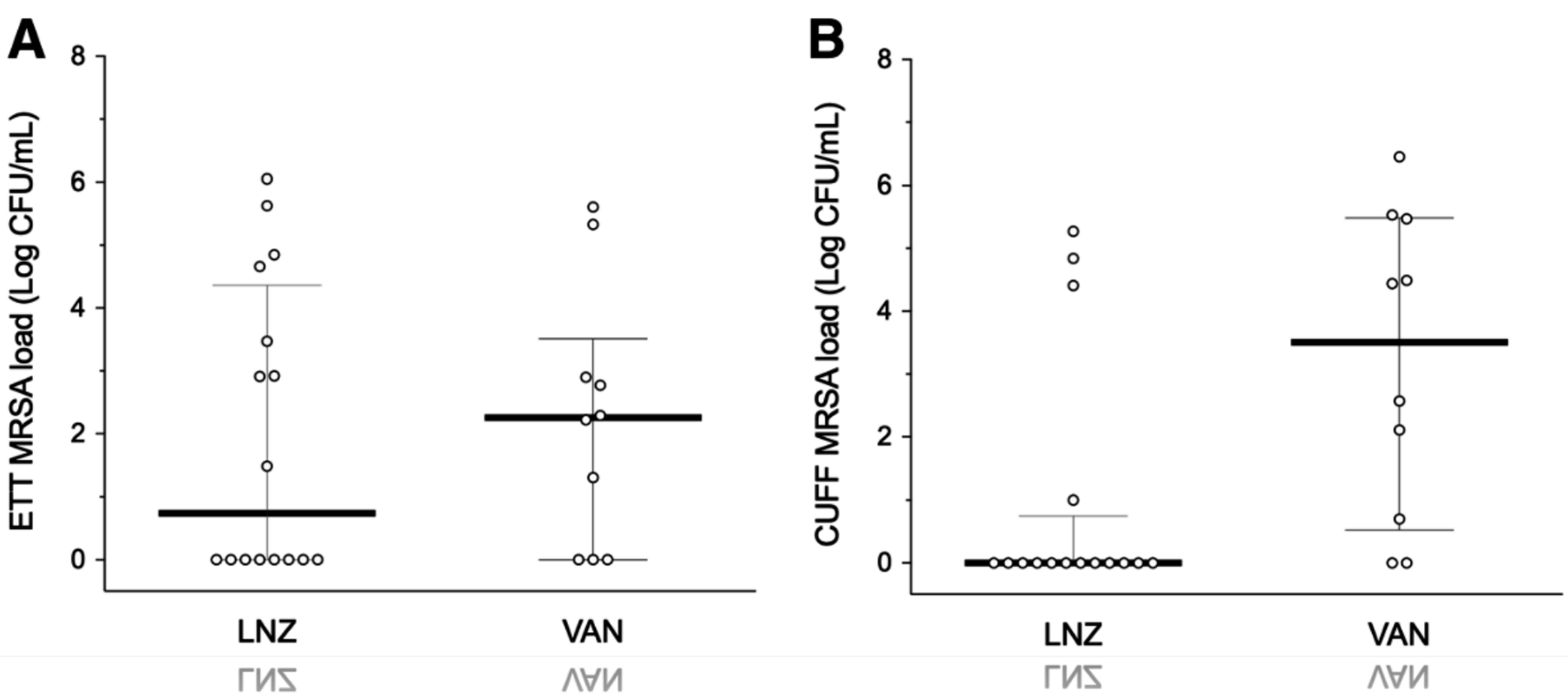
- Sono state segnalate con gli antibiotici chinolonici e fluorochinolonici reazioni avverse invalidanti, di lunga durata e potenzialmente permanenti, principalmente a carico del sistema muscoloscheletrico e del sistema nervoso.
- Di conseguenza, sono stati rivalutati i benefici ed i rischi di tutti gli antibiotici chinolonici e fluorochinolonici e le loro indicazioni nei paesi dell'UE.
- I medicinali contenenti cinoxacina, flumechina, acido nalidixico e acido pipemidico verranno ritirati dal commercio.
- **Non** prescriva questi medicinali:
  - per il trattamento di infezioni non gravi o autolimitanti (quali faringite, tonsillite e bronchite acuta);
  - per la prevenzione della diarrea del viaggiatore o delle infezioni ricorrenti delle vie urinarie inferiori;
  - per infezioni non batteriche, per esempio la prostatite non batterica (cronica);
  - per le infezioni da lievi a moderate (incluse la cistite non complicata, l'esacerbazione acuta della bronchite cronica e della broncopneumopatia cronica ostruttiva – BPCO, la rinosinusite batterica acuta e l'otite media acuta), a meno che altri antibiotici comunemente raccomandati per queste infezioni siano ritenuti inappropriati ;
  - ai pazienti che in passato abbiano manifestato reazioni avverse gravi ad un antibiotico chinolonico o fluorochinolonico.
- Prescriva questi medicinali con **particolare prudenza** agli anziani, ai pazienti con compromissione renale, ai pazienti sottoposti a trapianto d'organo solido ed a quelli trattati contemporaneamente con corticosteroidi, poiché il rischio di tendinite e rottura di tendine indotte dai fluorochinoloni può essere maggiore in questi pazienti. Dev'essere evitato l'uso concomitante di corticosteroidi con fluorochinoloni.

Comparative efficacy of linezolid and vancomycin for endotracheal tube MRSA biofilms from ICU patients

Fernández-Barat L et al Crit Care 2019

***Purpose**: To compare the efficacy of systemic treatment with linezolid (LNZ) versus vancomycin (VAN) on MRSA burden and eradication in endotracheal tube (ETT) biofilm and ETT cuff from orotracheally intubated patients with MRSA respiratory infection*

A prospective observational clinical study … 25 patients, 15 treated with LNZ and 10 with VAN, were included in the study



Current Treatment Options for MDR-GNB in critically-ill ptz

adapted by **Bassetti M** et al Frontiers in Medicine apr 2019

CRE

- Ceftazidime/avibactam (as preferred empirical choice when both KPC and OXA carbapenemases are reported locally) or meropenem/vaborbactam
- Although in the lack of high-level evidence, for both empirical and targeted treatment a combination with old (colistin, polymyxin B, tigecycline, old aminoglycosides, fosfomycin) or novel agents (plazomicin, eravacycline, double BL-BLI combinations) could be considered in the attempt of delaying emergence of resistance, after having carefully balanced potential additional toxicity on a case-by-case basis (expert opinion)
- In case of resistance to novel BL-BLI, consider polymyxins-based or aminoglycosides-based combinations with carbapenems and/or (tigecycline or eravacycline) and/or fosfomycin
- Consider concomitant administration of inhaled polymyxins/aminoglycosides when they are used intravenously for VAP

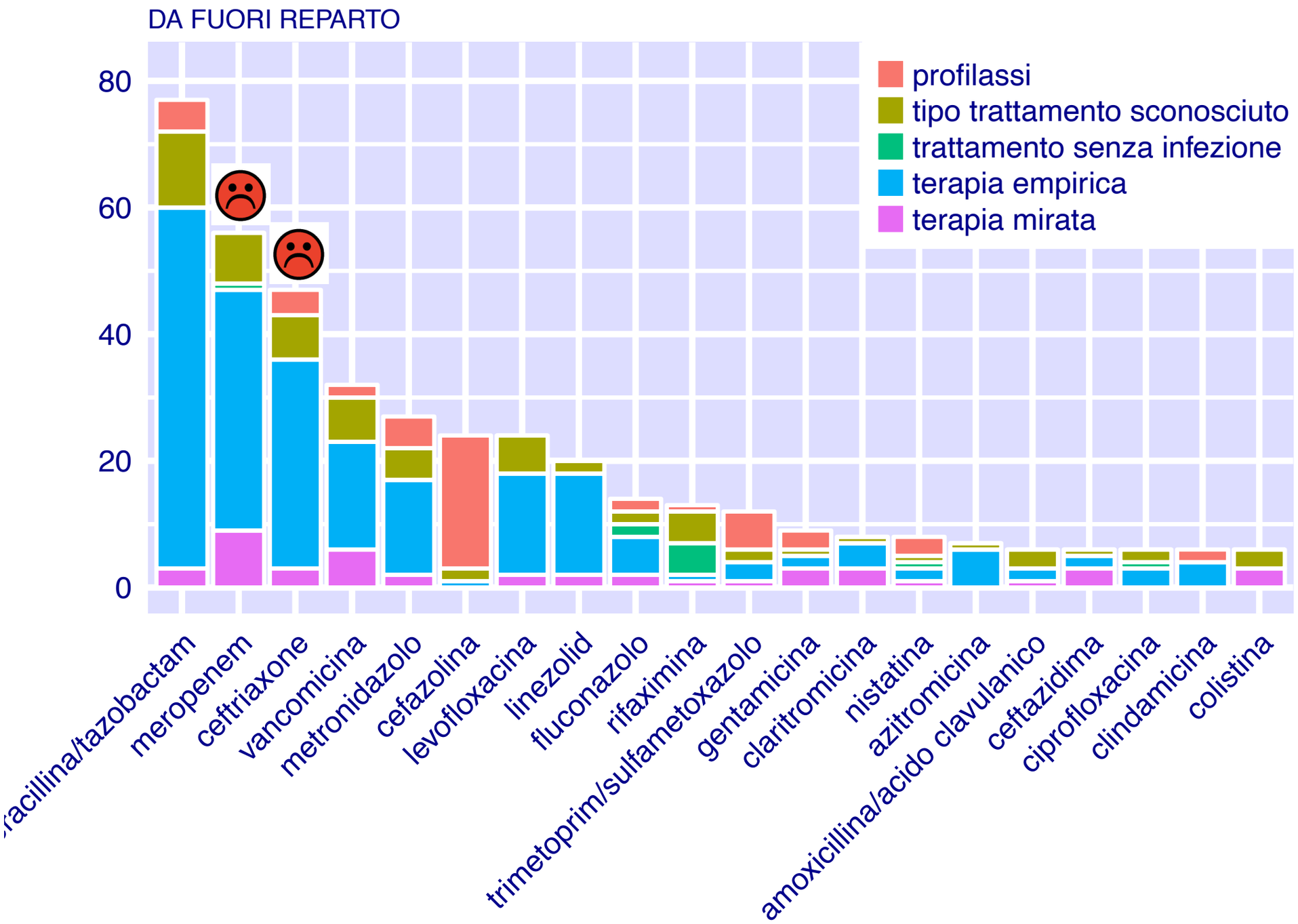
CRPA

- Ceftolozane/tazobactam (as preferred empirical choice in absence of concomitant risk of CRE) or ceftazidime/avibactam
- For empirical therapy, administer a second anti-pseudomonal agent (an aminoglycoside or a polymyxin or fosfomycin)
- Although in the lack of high-level evidence, for targeted therapy combination with old (colistin, polymyxin B, old aminoglycosides, fosfomycin) or novel agents (plazomicin, double BL-BLI combinations) could be considered in the attempt of delaying emergence of resistance, after having carefully balanced potential additional toxicity on a case-by-case basis (expert opinion)
- In case of resistance to novel BL-BLI, consider polymyxins-based or aminoglycosides-based combinations with carbapenems and/or fosfomycin and/or rifampin
- Consider concomitant administration of inhaled polymyxins/aminoglycosides when they are used intravenously for VAP

CRAB

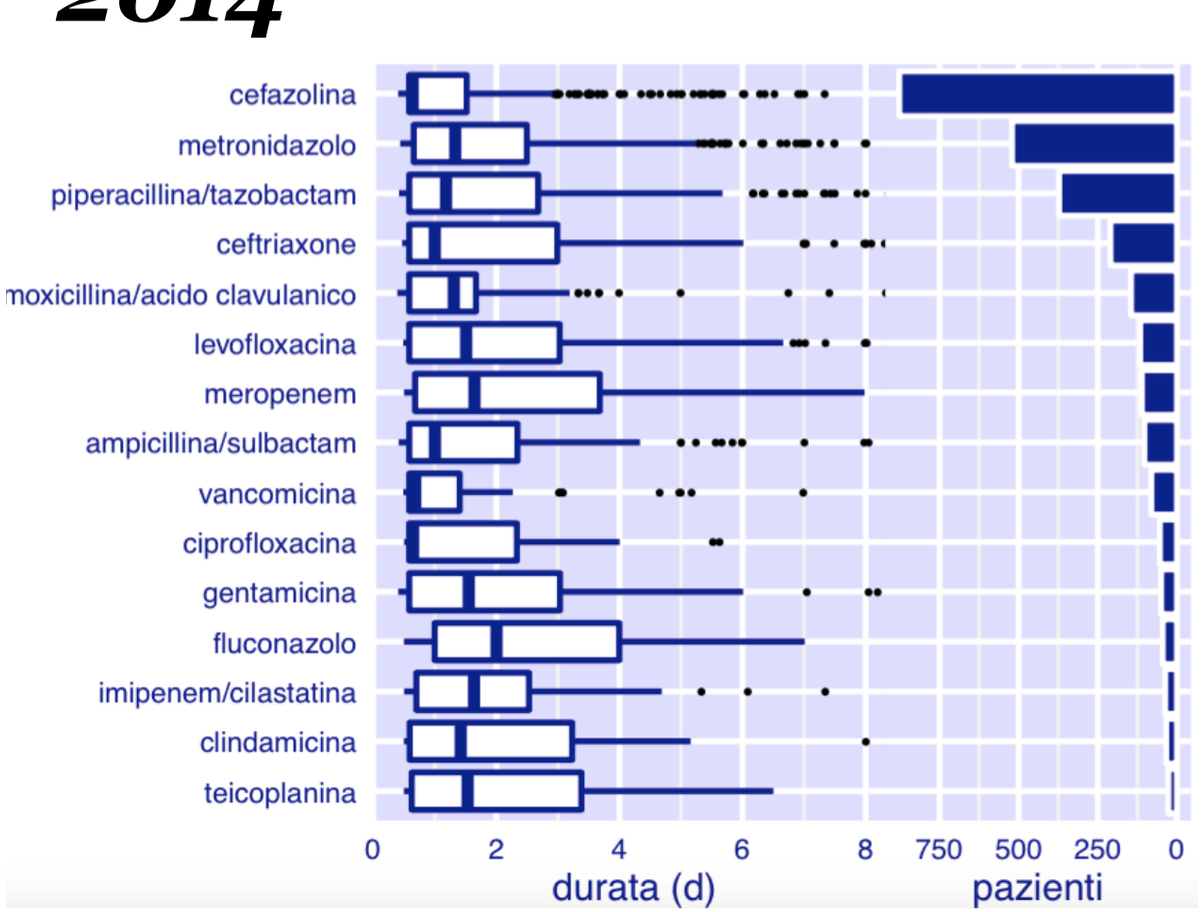
- Administer a polymyxin as the backbone agent
- Consider combination with old (carbapenems, old aminoglycosides, tigecycline, fosfomycin, rifampin) or novel agents (plazomicin, eravacycline)
- Consider concomitant administration of inhaled polymyxins/aminoglycosides when they are used intravenously for VAP

Numero di trattamenti antibiotici ereditati dai reparti di provenienza **2019**

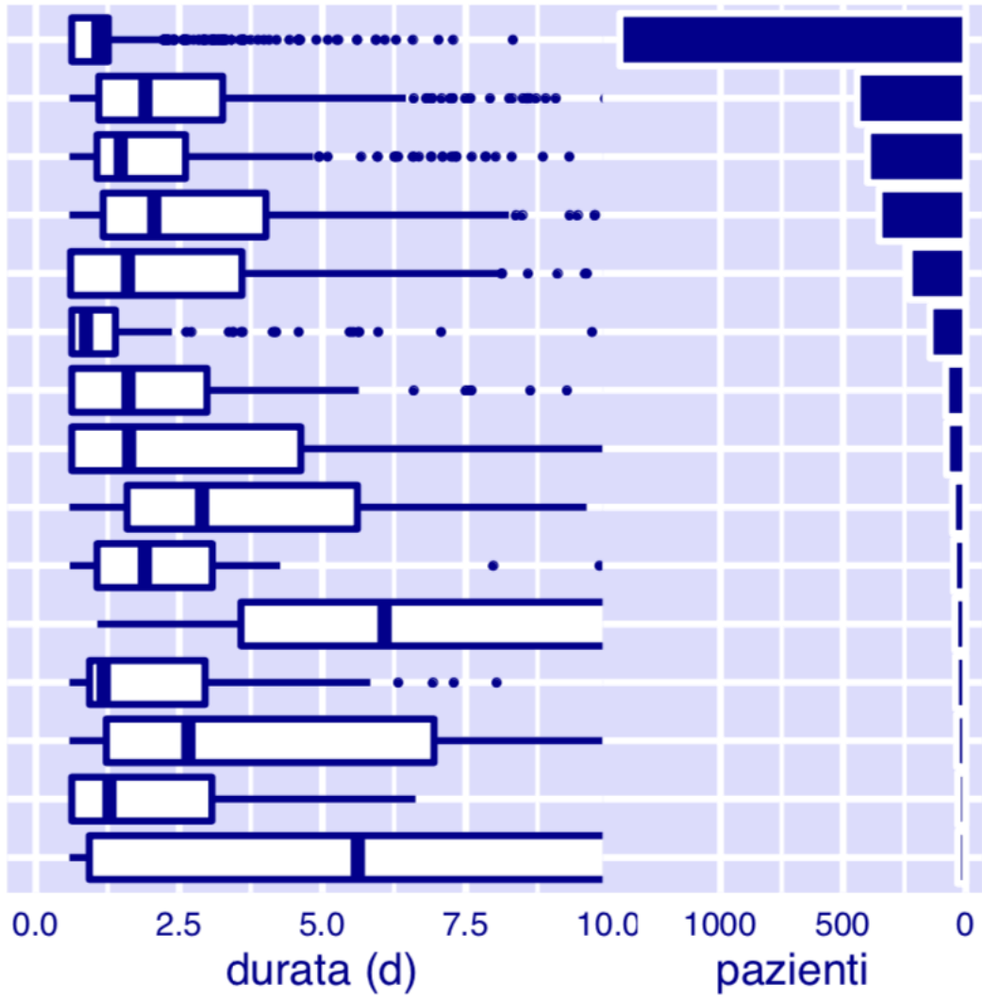


Durata delle **profilassi** per le 15 molecole più utilizzate

Report Antibiotici



2014



2019

GiViTI Gruppo italiano per la Valutazione degli interventi in Terapia Intensiva

Report Antibiotici

m3 margherita GiViTI — PROSAFE GiViTI

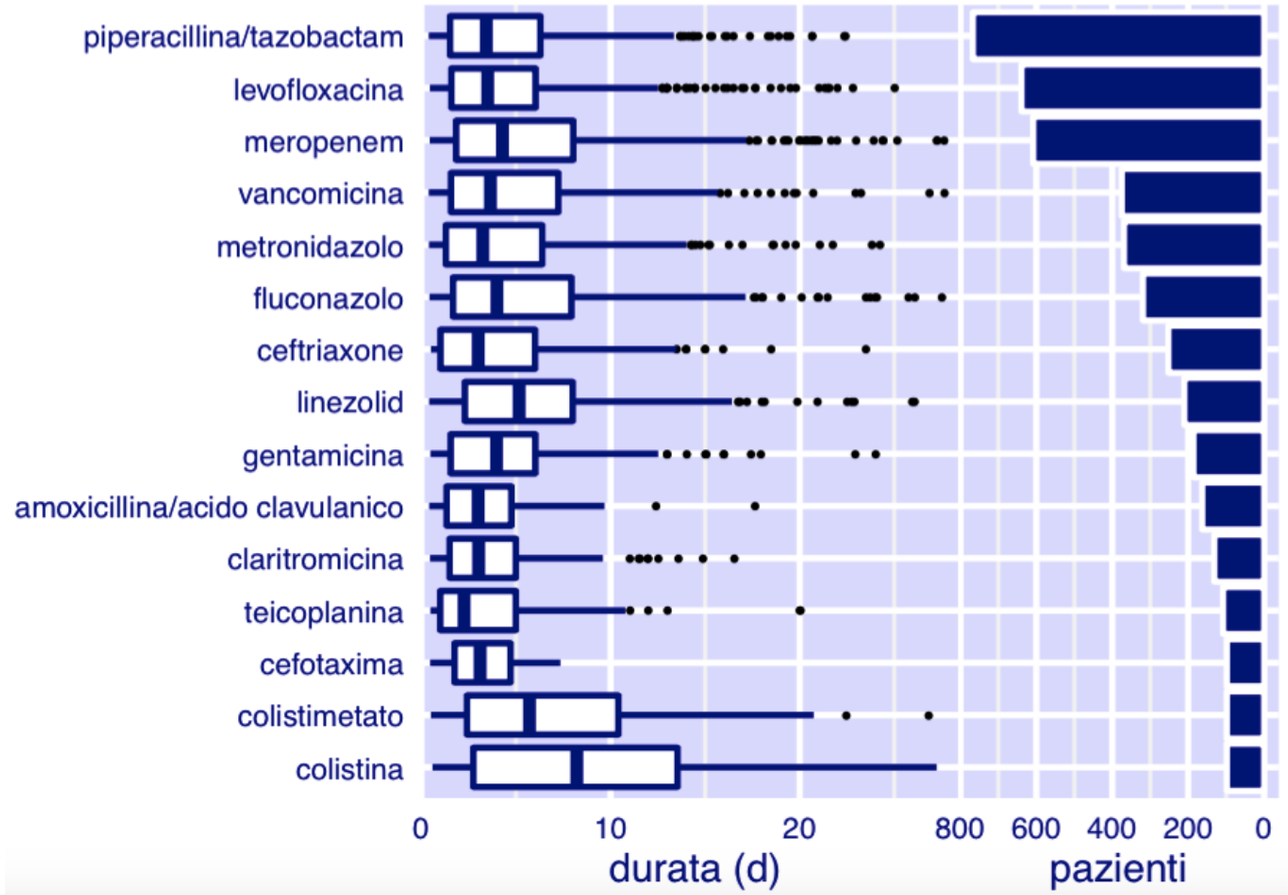
dal 2019-01-01 al 2019-12-31

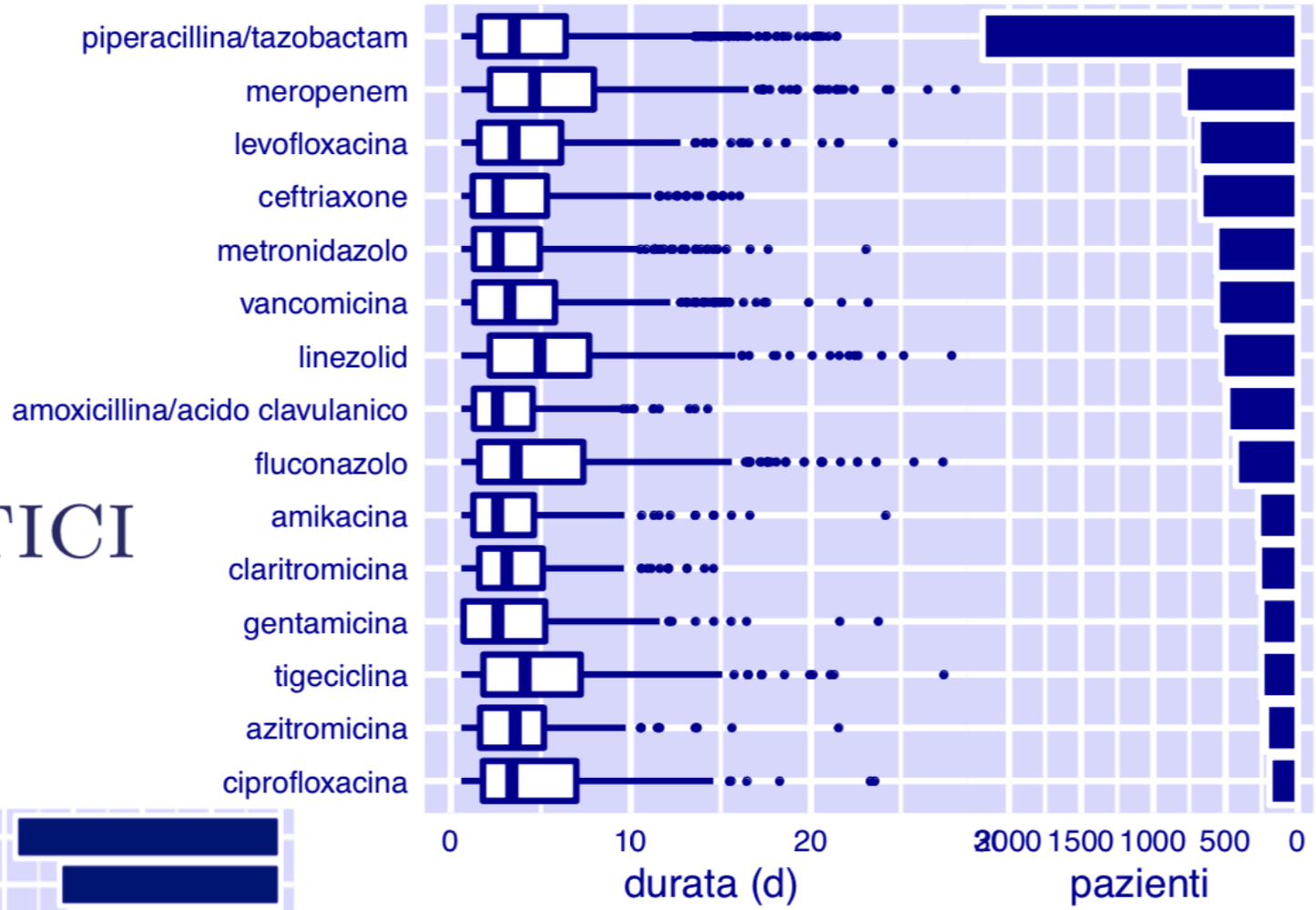
Centro di Coordinamento GiVITI
IRCCS – Istituto di Ricerche Farmacologiche Mario Negri
Villa Camozzi – Ranica (Bergamo)

Durata totale delle terapie antibiotiche (**empirica** o **mirata**) per le 15 molecole più utilizzate

Report Antibiotici

2014





2019

GiViTI Gruppo italiano per la Valutazione degli interventi in Terapia Intensiva

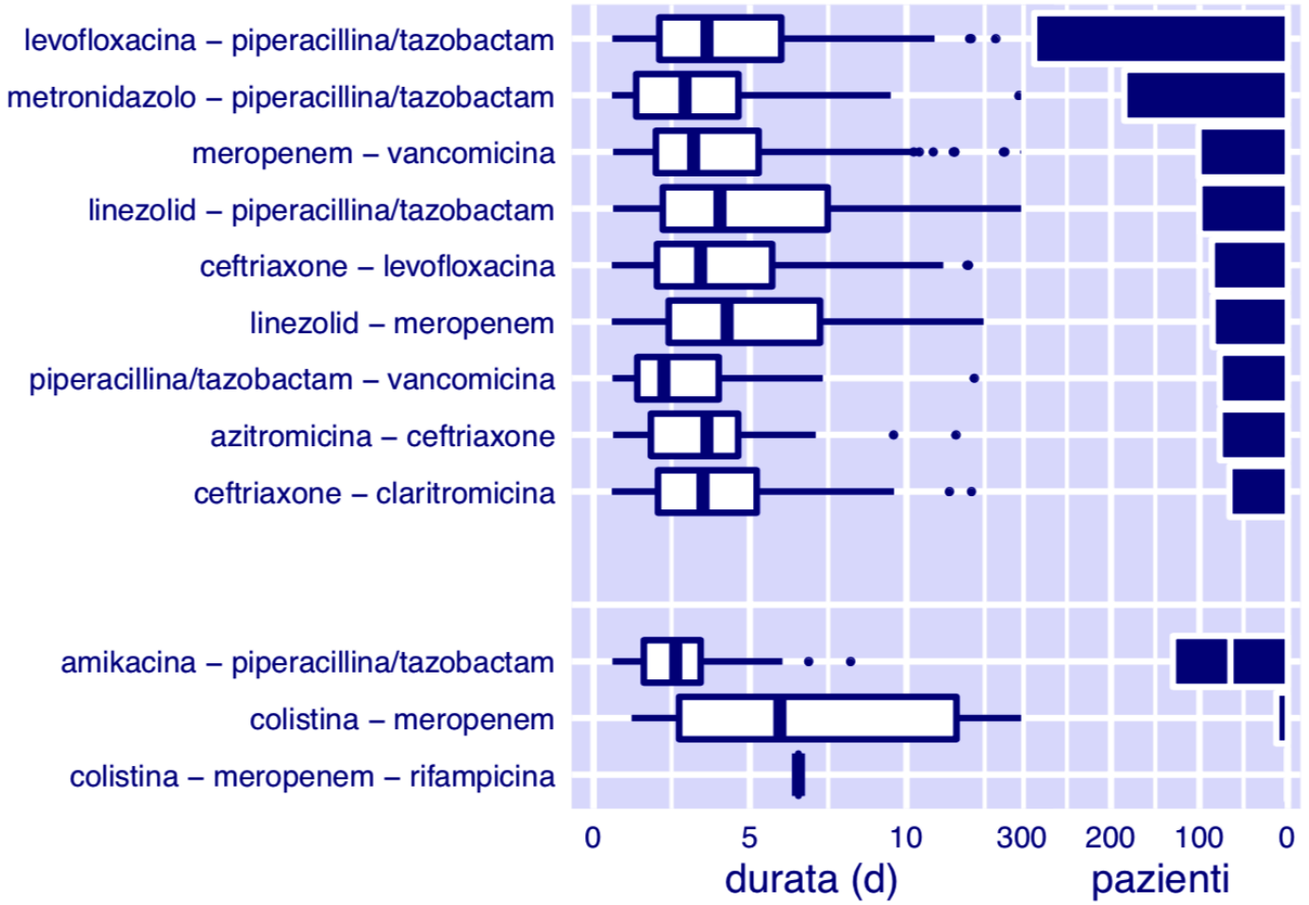
Report Antibiotici

m3 margherita GiViTI — PROSAFE GiViTI

dal 2019-01-01 al 2019-12-31

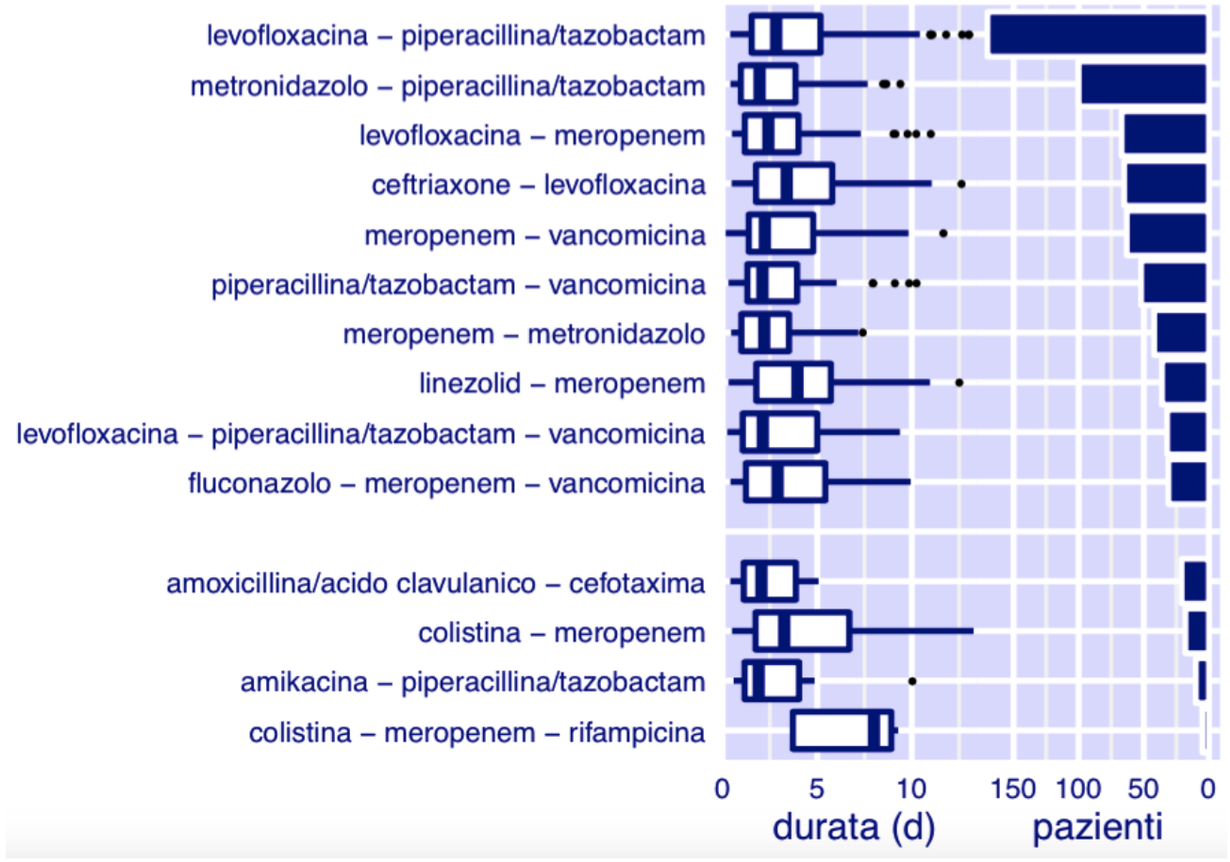
Centro di Coordinamento GiViTI
IRCCS – Istituto di Ricerche Farmacologiche Mario Negri
Villa Camozzi – Ranica (Bergamo)

Durata totale delle **associazioni** in terapia (empirica o mirata) per le 10 associazioni più utilizzate (in alto) e per tre associazioni clinicamente rilevanti (in basso)



Report Antibiotici

2014



2019

GiViTI Gruppo italiano per la Valutazione degli interventi in Terapia Intensiva

Report Antibiotici

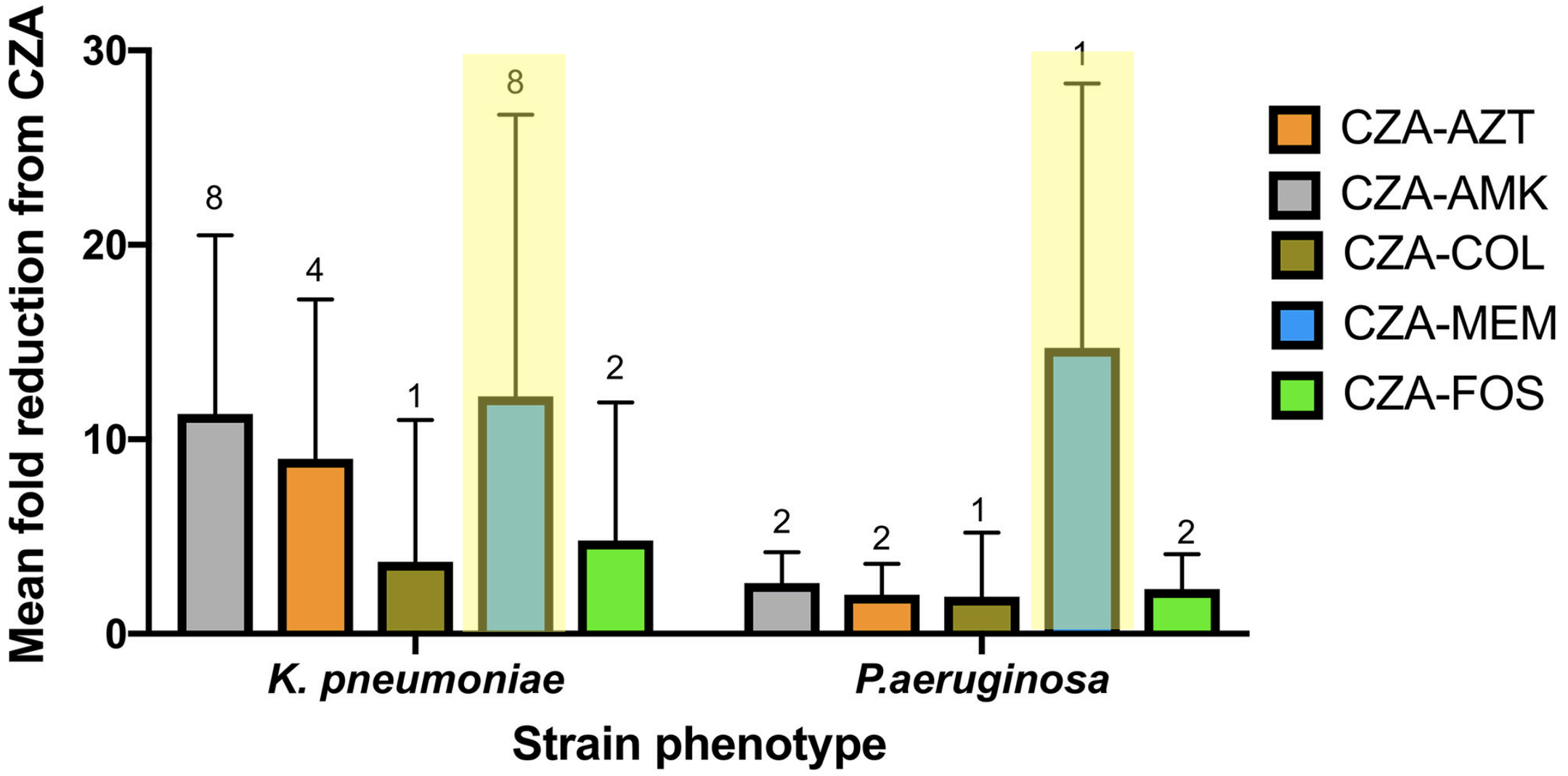
m3 margherita GiViTI — PROSAFE GiViTI

dal 2019-01-01 al 2019-12-31

Centro di Coordinamento GiViTI
IRCCS – Istituto di Ricerche Farmacologiche Mario Negri
Villa Camozzi – Ranica (Bergamo)

Mikhall S et al F Antimicrob Agents Chemother Aug 2019

Compared to CZA alone, we observed a **4-fold decrease in CZA MICs** for a majority of K. pneumoniae strains and at least a **2-fold decrease** for most P. aeruginosa isolates in the majority of combinations tested. In both P. aeruginosa and K. pneumoniae strains, CZA in combination with **AMK** or **AZT** was synergistic (2.15-log10 CFU/ml decrease). **CZA-MEM** was effective against P. aeruginosa and **CZA-FOS** was effective against K. pneumoniae



In vitro investigation of synergy among fosfomycin and parenteral antimicrobials against carbapenemase-producing Enterobacteriaceae

Avery LM et al Diagn Microbiol Infect Dis Nov 2019

Antibiotic interactions were defined as synergistic (FICI ≤0.50), additive (FICI N0.50 to ≤1.00), indifferent (FICI N1.00 to ≤4.00), or antagonistic (FICI N4.00)

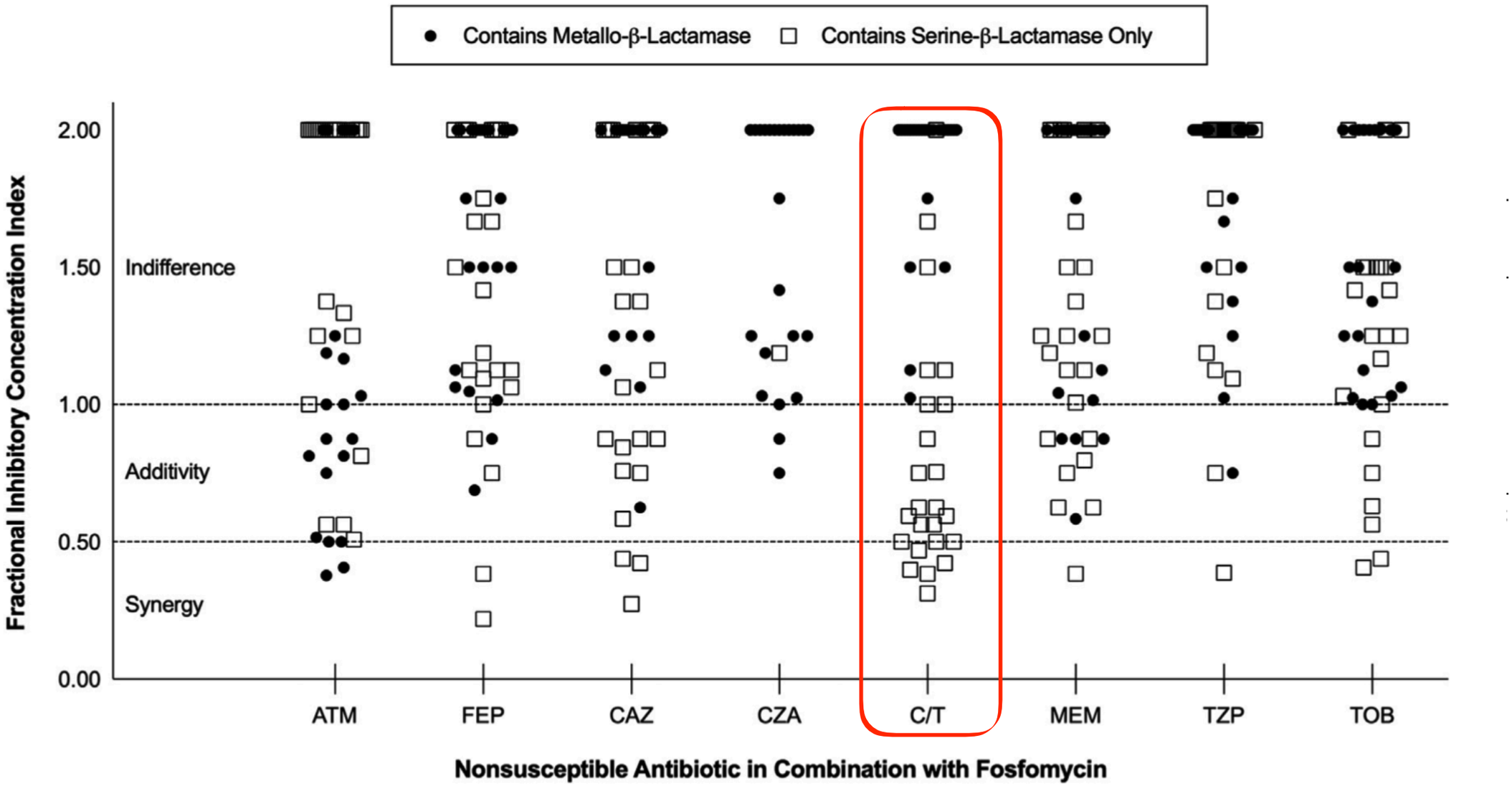
Table 3
Antibiotic interactions of various antimicrobials with fosfomycin.

	Nonsusceptible antibiotics tested in combination with FOF								
	ATM	FEP	CAZ	CZA	C/T	MEM	TZP	TOB	Total
Synergy, *N*	4	2	3	0	8	1	1	2	21
Synergy, %	8.3	4.1	6.1	0.0	16.3	2.0	2.0	4.4	5.8
Additive, *N*	13	5	8	3	11	10	2	7	59
Additive, %	27.1	10.2	16.3	11.5	22.5	20.4	4.1	15.6	16.2
Indifferent, *N*	31	42	38	23	30	38	46	36	284
Indifferent, %	64.6	85.7	77.6	88.5	61.2	77.6	93.9	80.0	77.8
FICI, geometric mean	1.25	1.42	1.38	1.56	1.15	1.37	1.68	1.31	NA
FICI, range	0.38–2.00	0.22–2.00	0.27–2.00	0.75–2.50	0.31–2.00	0.38–2.00	0.39–2.00	0.41–2.00	NA

MIC = minimum inhibitory concentration; ATM = aztreonam; FEP = cefepime; FOF = fosfomycin; CAZ = ceftazidime; CZA = ceftazidime/avibactam; C/T = ceftolozane/tazobactam; MEM = meropenem; TZP = piperacillin/tazobactam; TOB = tobramycin; FICI = fractional inhibitory concentration index; NA = not applicable.

In vitro investigation of synergy among fosfomycin and parenteral antimicrobials against carbapenemase-producing Enterobacteriaceae

Avery LM et al Diagn Microbiol Infect Dis Nov 2019



HOW to optimize treatment of Carbapenem-Resistant Enterobacteriaceae (CRE)

Optimized treatment for CRE

Empiric treatment

Risk factors

- Known colonisation or prior infection (or roomate infected) by Enterobacteriaceae strain producing KPC or OXA-48≠

OR

- Local epidemiology (or recent hospitalization in settings) with more than 20-25% prevalence of carbapenem-producing and ESBL-producing Enterobacteriaceae

PLUS any of the following:

- Prior use of carbapenems and/or colistin
- ICU admission or long admission in hospital wards
- Severe hospital-acquired infection (bacteremia, septic shock)
- Immunossuppression, multiple comorbidities

Definitive treatment

Microbiology results

- Identification,
- Susceptibility testing
- Detection of resistance mechanisms

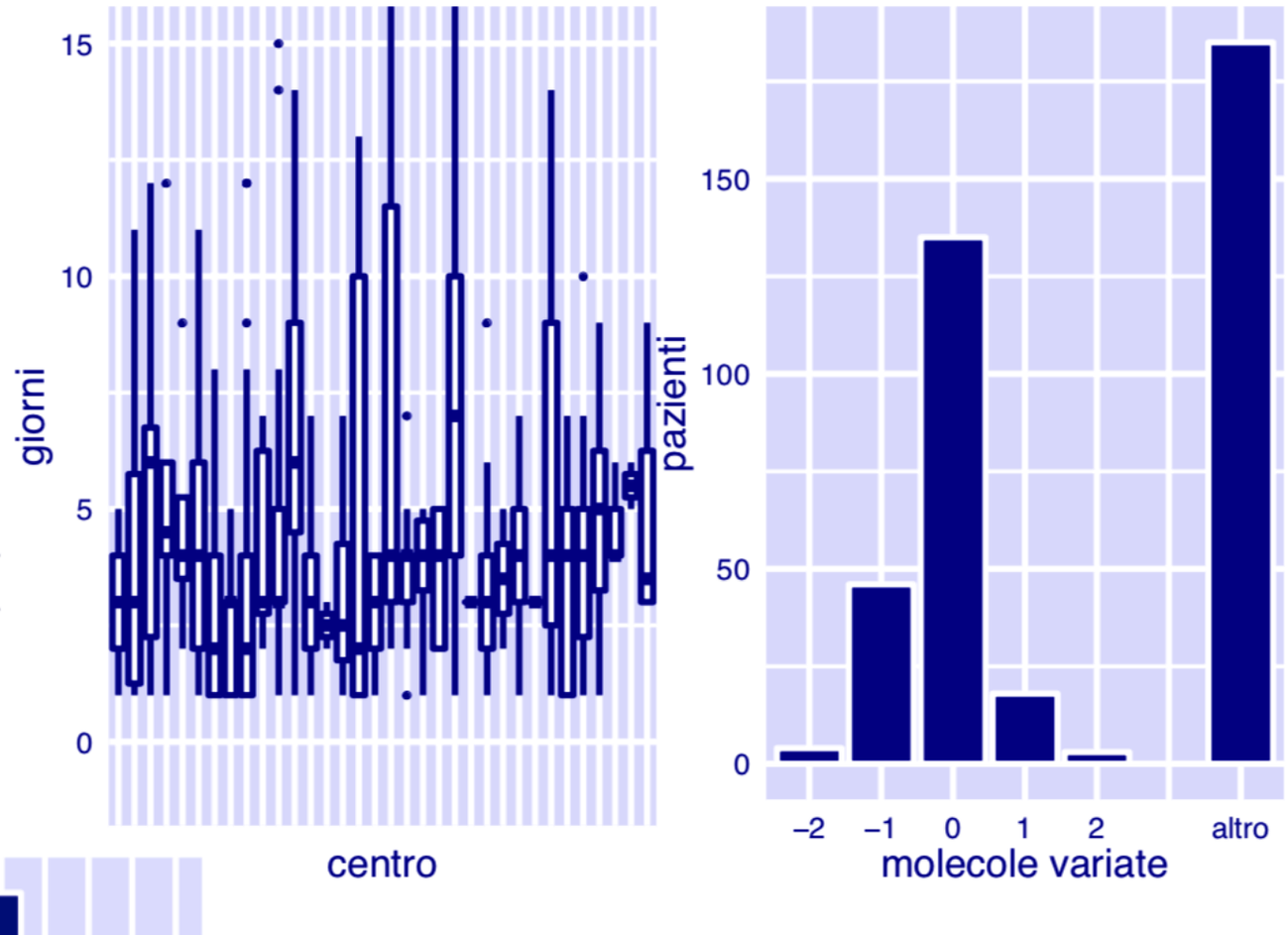
[KPC, OXA, MBL (NDM, VIM, etc), double mechanisms]

- Determination of MICs for: carbapenems, colistin, fosfomycin, aminoglycosides and all new antibiotics (CAZ/AVI, MER/VAB, plazomicin, etc)

Combination* regimen (double or triple) to increase probability of adequate initial		**Monotherapy or combination treatment based on patient's, pathogen's and antibiotic's parameters** (Figure 1)		
CAZ/AVI or MER/VAB based combination*	**Colistin based combination* (double or triple)**	**Monotherapy** (prerequisites in Figure 1)	**CAZ/AVI ^ or MER/VAB^ based combination***	**Colistin based combination* (double or triple) For MBL, and KPC or OXA resistant to CAZ/AVI, MER/VAB**
Gentamicin or other aminoglycoside	Carbapenem (if epidemiological data witness MICs ≤16 mg/L)	CAZ/AVI	Gentamicin or other aminoglycoside	Carbapenem (subject to MIC ≤16 mg/L)△
Fosfomycin	Gentamicin or other aminoglycoside	MER/VAB	Fosfomycin	Gentamicin or other aminoglycoside
Colistin	Fosfomycin	Colistin	Colistin	Fosfomycin
Tigecycline	Tigecycline	Aminoglycoside	Tigecycline	Tigecycline
				Double carbapenem

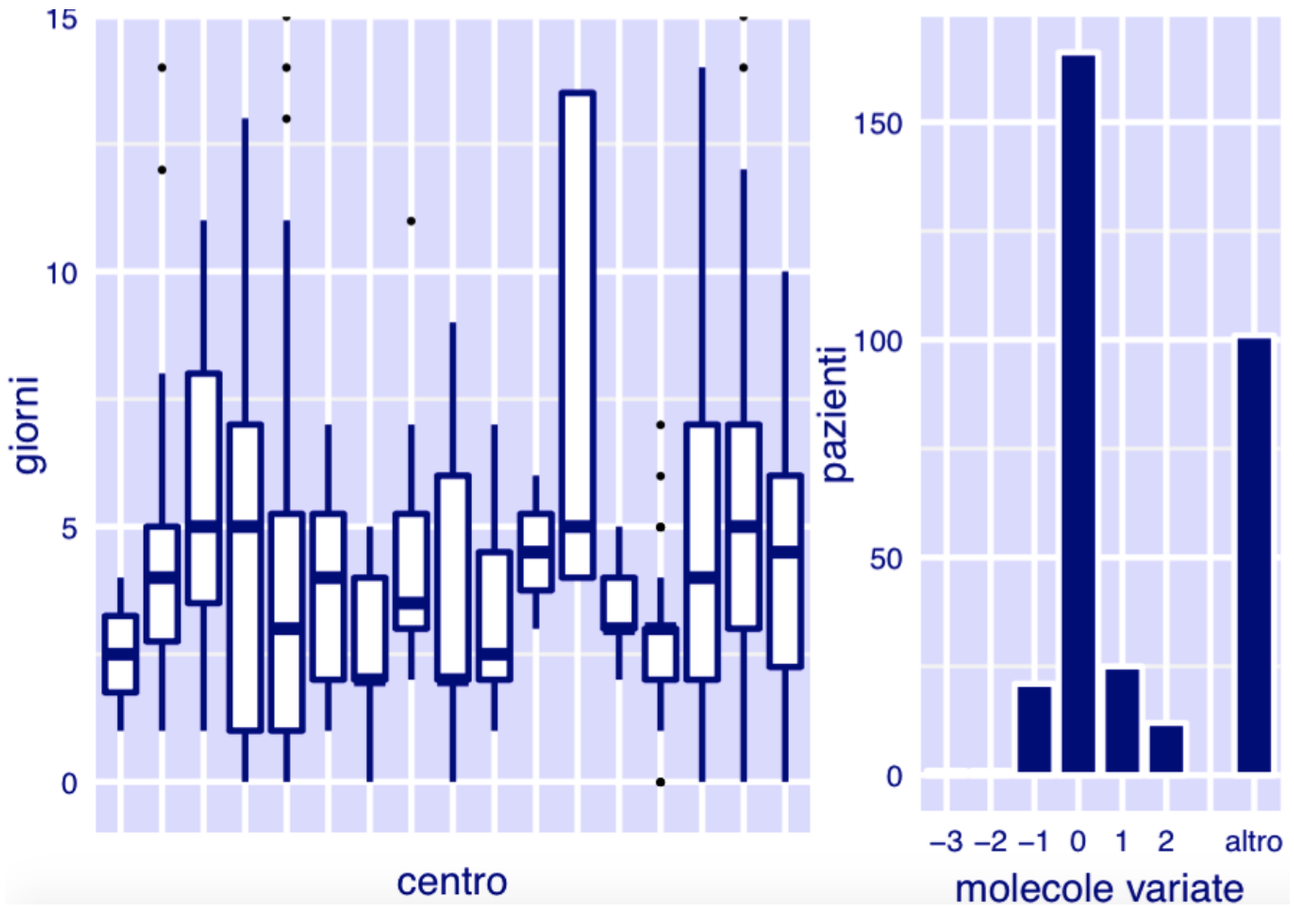
Gruppo italiano per la Valutazione degli interventi in Terapia Intensiva - uso e consumo degli ATB, quali novità in 5 anni

Durata della **terapia empirica** prima del passaggio a **terapia mirata**



Report Antibiotici

2014



2019

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Come posso ottimizzare una terapia empirica? E quali sono gli elementi da considerare?

Determinants of the empirical choice of antibiotics

(questions to be answered before prescription of an antibiotic)

The pathogen and risk factors for MDRO

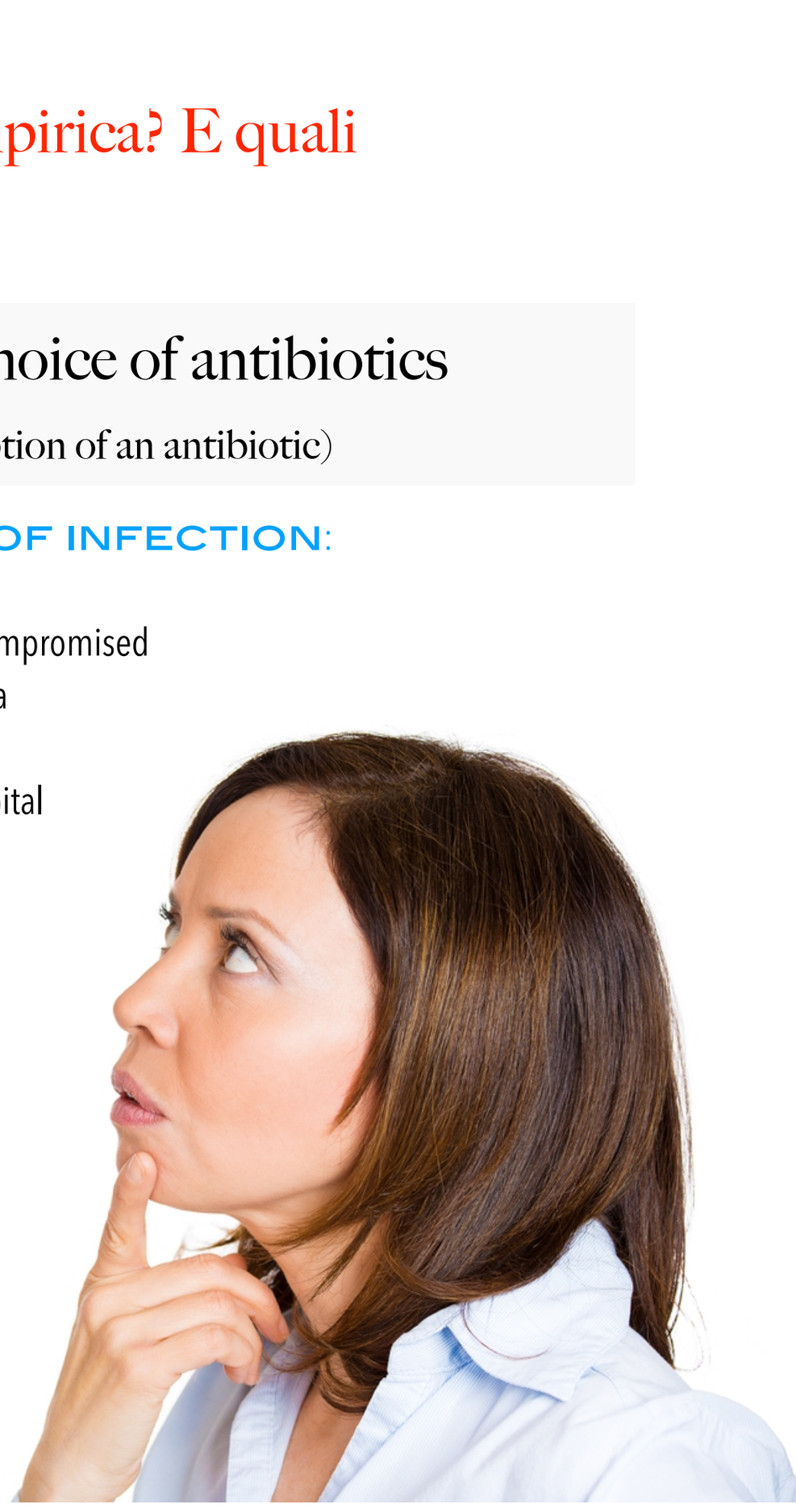
- ANATOMICAL SITE OF INFECTION:
  potential pathogens
- immunocompetent vs immunocompromised
- colonisation with resistant bacteria
- susceptibility patterns of potential pathogens in the community/hospital

antimicrobial dosing

- PK/PD properties
- LOADING DOSE
- Impact of CRRT

algorithms in decision making

- VAP/HAP
- KPC
- IAIs
- UTIs



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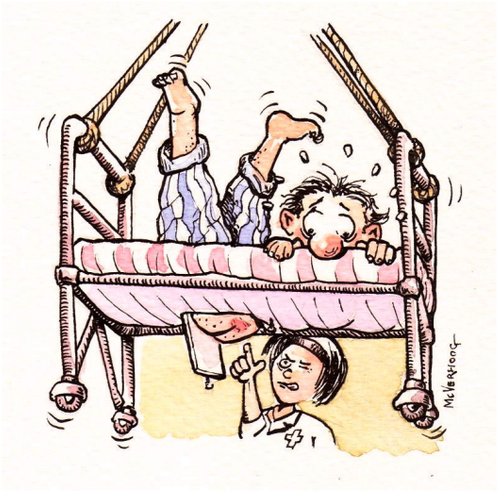
antimicrobial dosing

- **PK/PD** properties
- **LOADING DOSE**
- Impact of **CRRT**

Likely Antimicrobial Susceptibility and biomarkers

- **BROAD**-spectrum vs **NARROW**
- **NOVEL WAYS** to detect pathogens early
- **PCT** (PPV-NPV)

> Anatomical diagnosis is therefore crucial for the choice of empiric antibiotic treatment



Can routine surveillance samples from tracheal aspirate predict bacterial flora in cases of VAP?

Lampati L, Langer M et al Minerva Anestesiol 2009;75:555-62

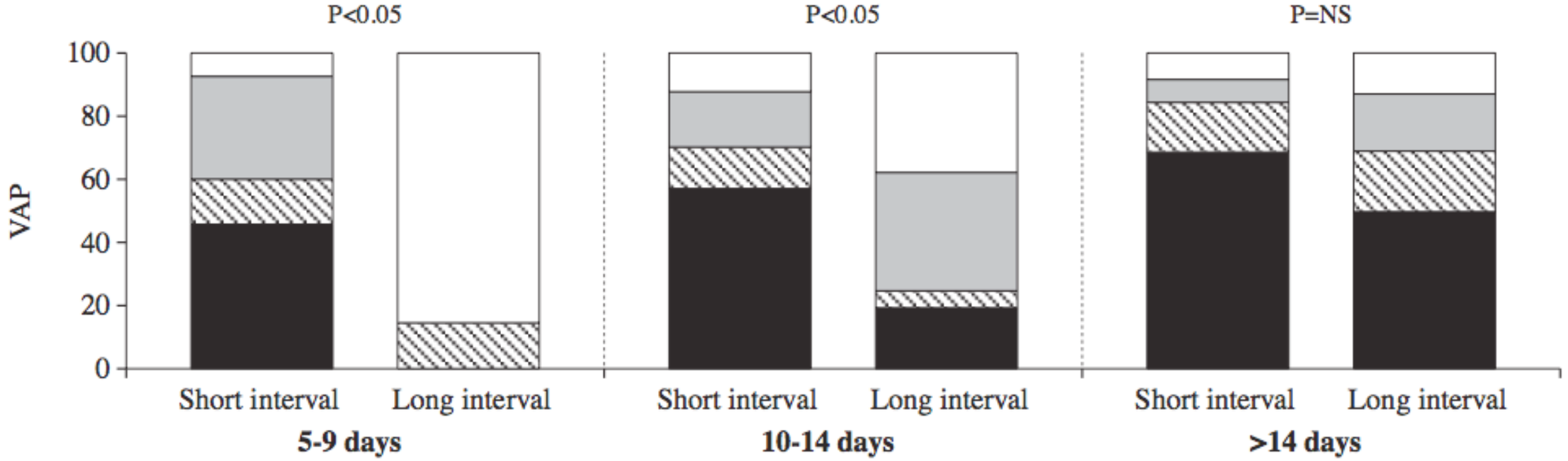
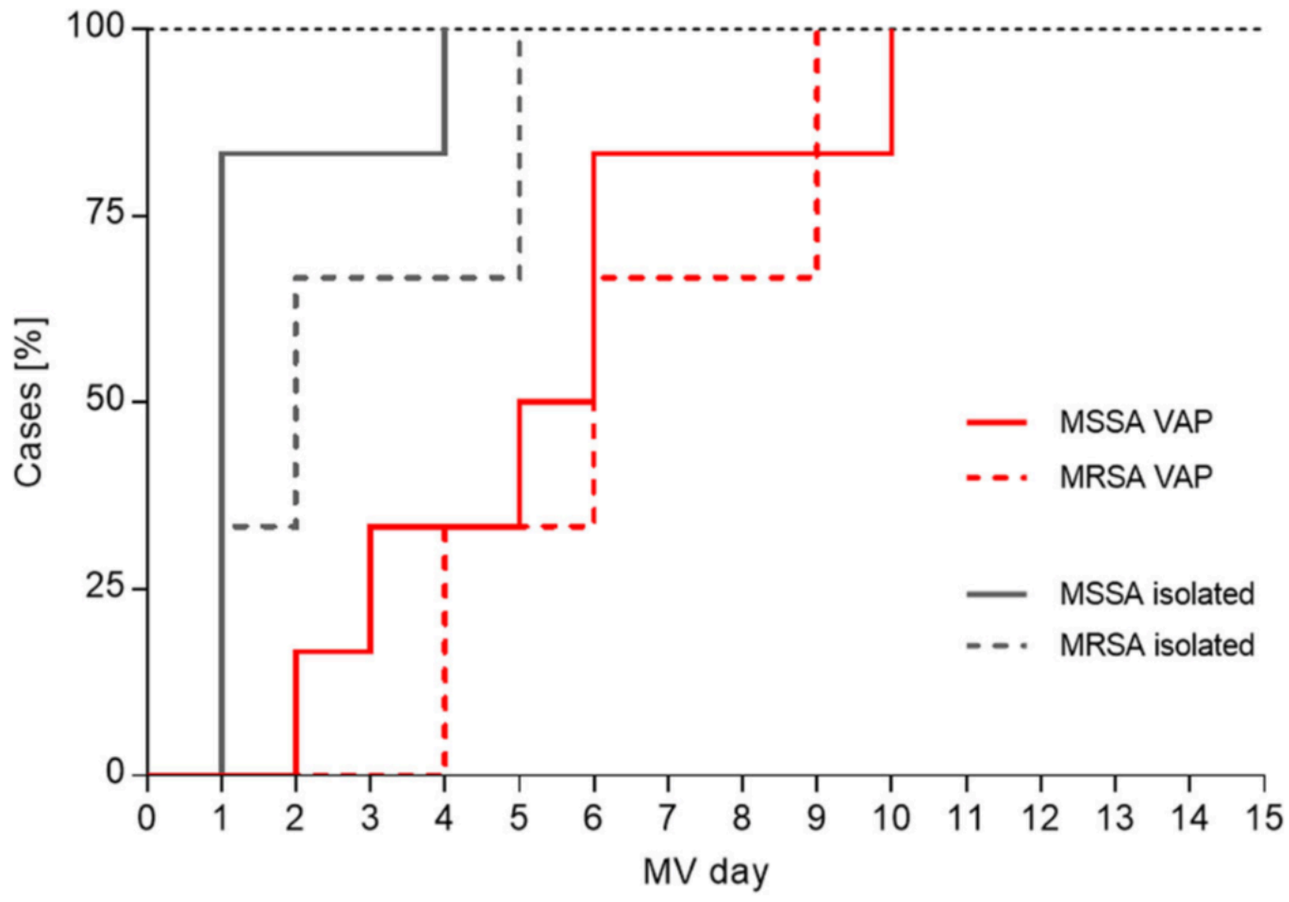


Figure 1.—Distribution of different TA results related to the 3 groups of VAP with different of respiratory support preceding VAP onset togheter with TA collect time. *Short interval:* the time elapsed between TA and VAP onset is 2-4 days. *Long Interval:* the time elapsed between TA and VAP onset is 5-8 days. *Black bars:* % of TA that showed all VAP responsible pathogens. *Cross-hatched bars:* % of TA that isolated pathogens completely different from VAP etiology. *White bars:* % TA without growth.

The utility of endotracheal aspirate bacteriology in identifying mechanically ventilated patients at risk for VAP

a single-center prospective observational study

Kabak E et al BMC Infect Dis 2019;19:756



Detection *of S. aureus in the ETA preceded S. aureus VAP by approximately* ***4 days****, while Gram-negative organisms were first detected* ***2.5 days*** *prior to Gram-negative VAP*

First detection of S. aureus lower airway colonization and progression to S. aureus VAP

The utility of endotracheal aspirate bacteriology in identifying mechanically ventilated patients at risk for VAP

a single-center prospective observational study

Kabak E et al BMC Infect Dis 2019;19:756

We found that approximately ***every third patient*** *with* ***heavy*** *S. aureus or Gram-negative colonization in SQ-ETA progressed to VAP with a corresponding pathogen. At the same time,* ***only every sixth patient lightly*** *colonized with S. aureus progressed to VAP, and no patient with Gram-negative light colonization did so*

Causes of poor clinical evolution or **therapeutic failure**

Alvarez-Lerma F et al Drugs, 2012

- Lack of activity in empirical use (inappropriate treatment)
- Severe immunosuppression in the host
- Concomitant diseases in advanced stage
- Related adverse effects
- **Underdosing**
- **Poor penetration in the infected tissue**

An evaluation of risk factors to predict target concentration non-attainment in critically ill patients prior to **empiric β-lactam**

Imani S et al Eur J Clin Microbiol Infect Dis aug 2018

- A total of 249 patients - piperacillin (169); meropenem (80) were investigated
- For non-CRRT patients (n = 210), multivariate analysis demonstrated the following: **male gender** (P = 0.006); **younger age** (P = 0.015); prescribed daily antibiotic dose less than 1.5 times the recommendations (P = 0.004); **lack of positive microbiology** (p = 0.006); **lower overall illness severity** (P = 0.005); and estimated **glomerular filtration rate** (eGFR) ≥ **90 mL/min/1.73 m²** (P < 0.001), to be associated with **$C_{min} \leq$ MIC**
- No predictor variable was found to be significantly associated with $C_{min} \leq$ MIC for the CRRT cohort

Antibiotic Dosing in Critically Ill Patients Receiving CRRT: **Underdosing is Overprevalent**

Lewis SJ and Mueller BA et al Semin Dial 2014

In CRRT patients our too-careful practice of "**starting low and going slow**" with antibiotic dosing to avoid the risk of toxicity may lead to an "**overprevalence**" of **antibiotic underdosing** and call for clinicians to strike a more aggressive antibiotic prescription in the intensive care unit

Renal Dosing of Antibiotics: Are We Jumping the Gun?

Crass RL et al Clin Infect Dis 2018

- Antibiotic renal dose adjustments are determined in subjects with **stable chronic kidney disease** and may not translate to patients in late phase trials and practice

- Ceftolozane/tazobactam, ceftazidime/avibactam, and telavancin all carry precautionary statements for reduced clinical response in patients with baseline creatinine clearance 30 – 50 mL/min, potentially due to unnecessary dose reduction in the setting of acute kidney injury (AKI)

- We identify AKI on admission in a substantial proportion of patients with pneumonia (27.1%), intra-abdominal (19.5%), urinary tract (20.0%), or skin and skin structure infections (9.7%) that **resolved by 48 hours in 57.2% of cases**

Acute kidney injury is **a dynamic perturbation** of renal steady-state

Augmented Renal Clearance

Cook AM et al Pharmacotherapy 2019;39(3):346-354

- ***Augmented renal clearance*** *(ARC) is a phenomenon in critically ill patients characterized by increased creatinine clearance and elimination of renally-eliminated medications*
- *Augmented renal clearance* ***is typically defined as*** *a urine creatinine clearance greater than normal values of* ***130 ml/min/1.73 m²*** *in males and* ***120 ml/min/1.73 m²*** *in females*
- *Augmented renal clearance is associated with* ***suboptimal exposure*** *to critical medications, including β-lactams and vancomycin, increasing the risk of treatment failure*

Population	Prevalence	Mean Creatinine clearance values
Burn[5]	65%	172.1 ml/min/1.73 m^2
Febrile neutropenia[72]	16.4%	157.4 ml/min/1.73 m^2
Sepsis[14, 42]	39.5-56%	154-210 ml/min/1.73 m^2
Subarachnoid hemorrhage[11]	100%	326 ml/min
Trauma[10]	85.7%	166 ml/min/1.73 m^2
Traumatic brain injury[9]	85%	179 ml/min/1.73 m^2 150 ml/min/1.73 m^2 (while not receiving CPP treatment)

Estimating Renal Function in Drug Development:

Time to Take the Fork in the Road

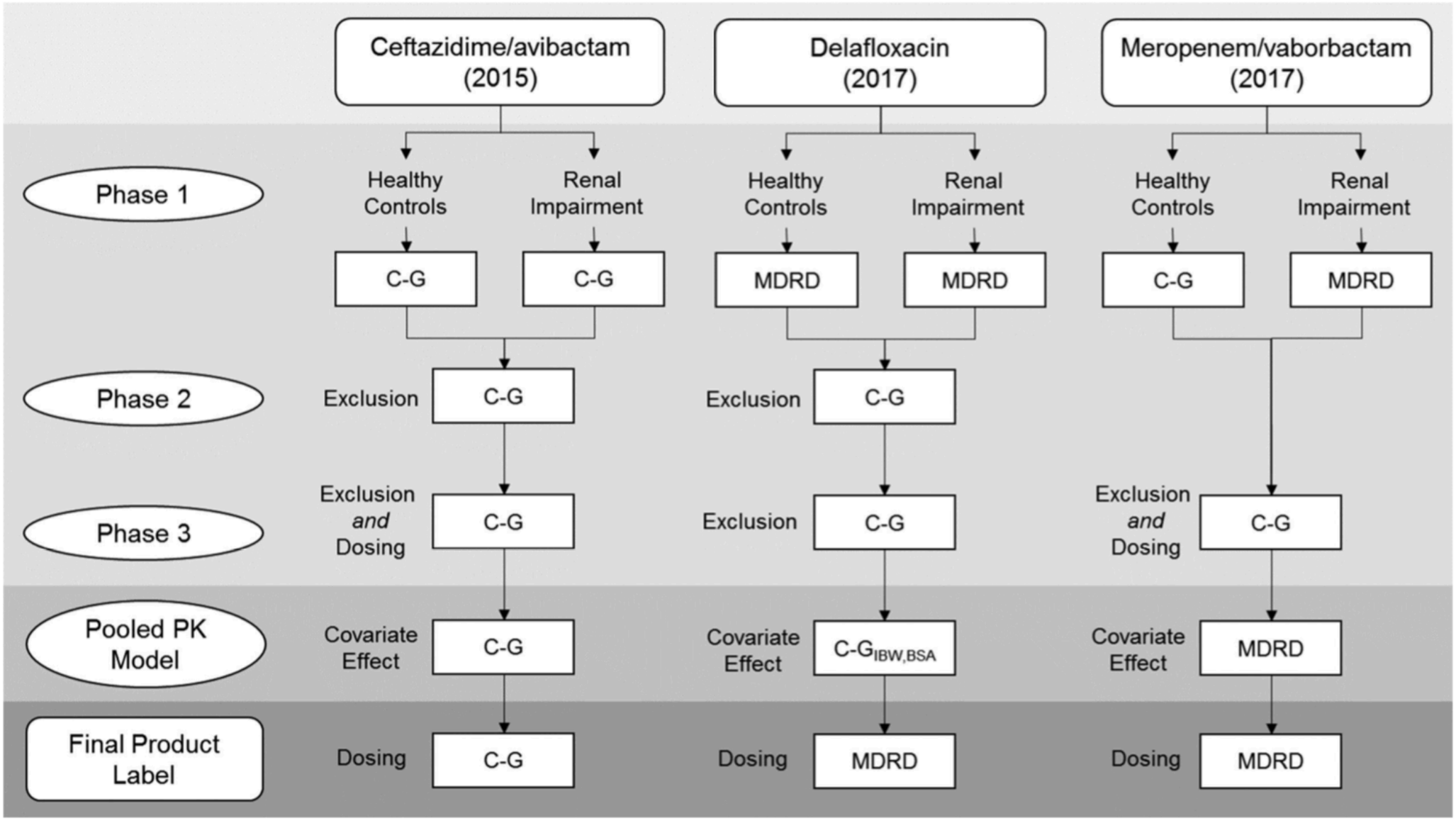


Figure 1. Assessment of renal function throughout the drug development process for the 3 systemically active antibiotics approved by the FDA since 2015. C-G, Cockcroft-Gault equation; C-$G_{IBW,BSA}$, Cockcroft-Gault equation calculated using the lesser of ideal and actual body weight and normalized to body surface area; MDRD, Modification of Diet in Renal Disease equation; PK, pharmacokinetic.

Quale formula utilizzare?

- ***Formula di Cockroft-Gault***

  ClCr[ml/min/1.73m^2] = (140-eta[anni] x Peso corpo- reo [Kg]) / Creatinina[mg/dl] x72 x 0.73 [se femmina] … *limite principale è che assume che il VFG aumenti con l'aumentare del peso … sovrastima il VFG …* ***non andrebbe più usata***

- ***Formula MDRD*** *(modification of diet in renal disease)*

  VFG [ml/min/1.73m^2] = 175 x Creatinina [mg/dl] $^{-1.154}$ x eta[anni] $^{-0.203}$ x 0.742 [se femmina] x 1.21 [se di colore] … molto più accurata del C-G nel predire il VFG … limite sottostima fino al 15% il VFG in soggetti con funzione normale

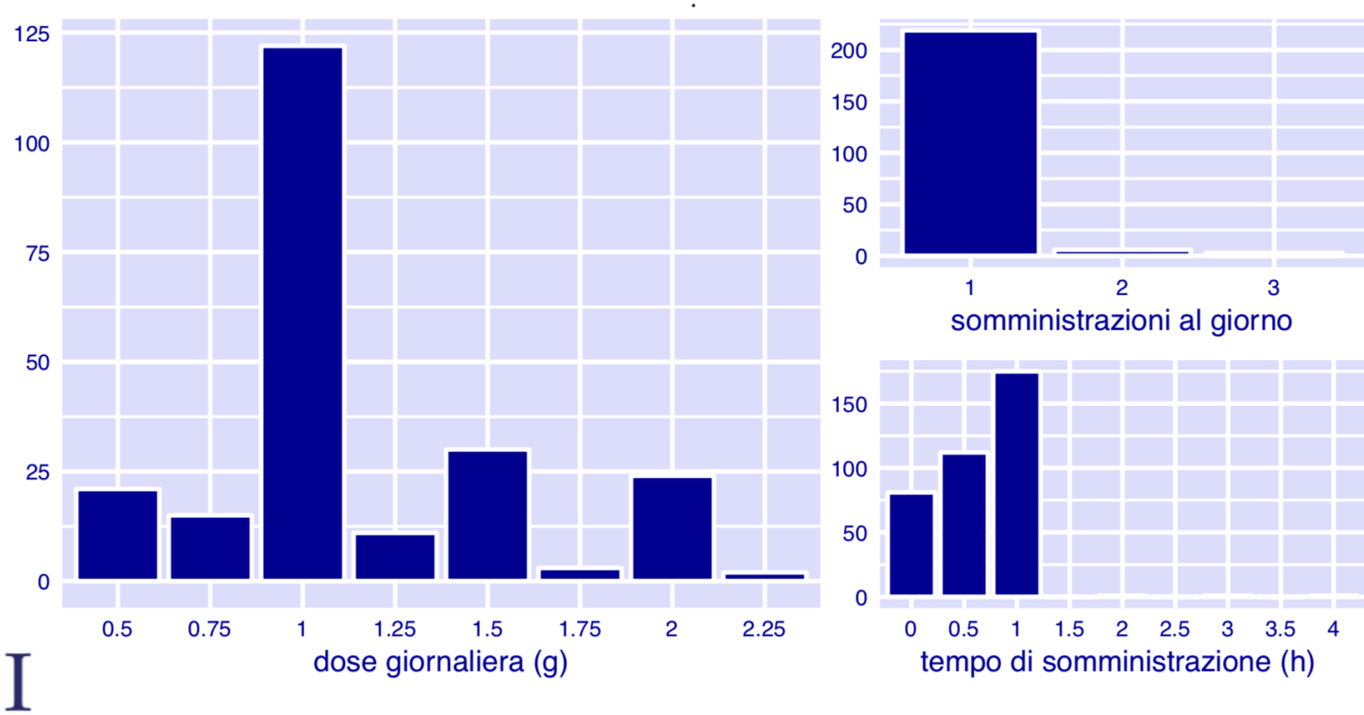
- ***Formula CKD-EPI*** *(chronic kidney disease epidemiology collaboration)*

  VFG [ml/min/1.73m2]= 141 X min (Scr/κ,1)α X max(Scr/κ,1)-1.209 X 0.993età[anni] X 1.018 [se fem- mina] X 1.159 [se di colore]

  Dove Scr è la creatininemia in mg/dL, κ è una costante pari a 0.7 per le femmine e 0.9 per i maschi, α è una costante pari a −0.329 per le femmine e −0.411 per i maschi, min indica il minimo fra Scr/κ ed 1, e max in- dica il massimo fra Scr/κ ed 1 …*La formula CKD-EPI in soggetti con VFG>60 ml/min/1.73m^2 fornisce valori di VFG significativamente superiori a quelli ottenuti con formula MDRD*

Finally, we suggest measuring GFR in phase 1 studies and employing the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to integrate data across clinical trials. This will help to harmonize CKD staging, population pharmacokinetic analyses, and dosing by estimated renal function .. **Crass RL** et al J Clin Pharmacol 2018

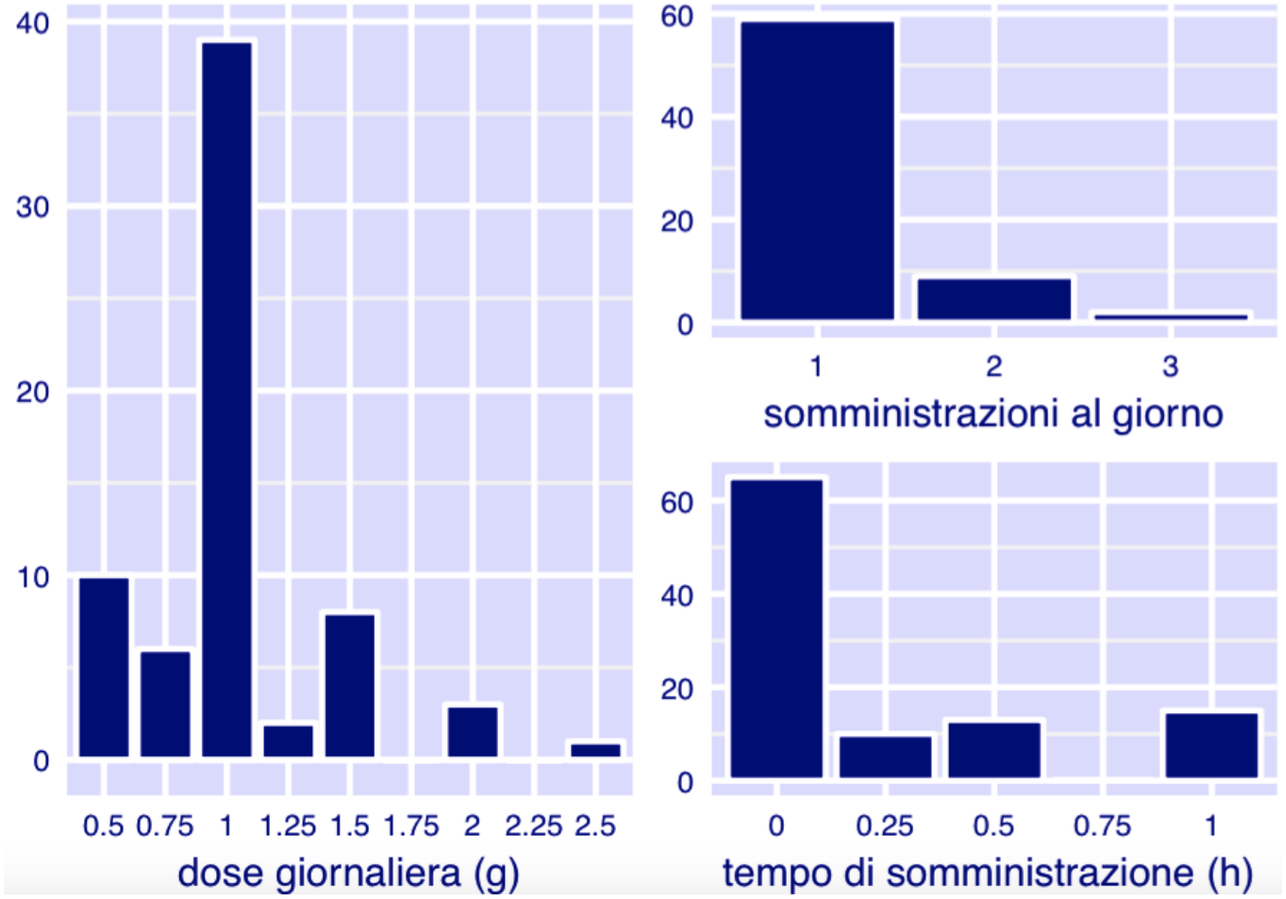
Strategia di somministrazione:
AMIKACINA



Report Antibiotici

2014

2019



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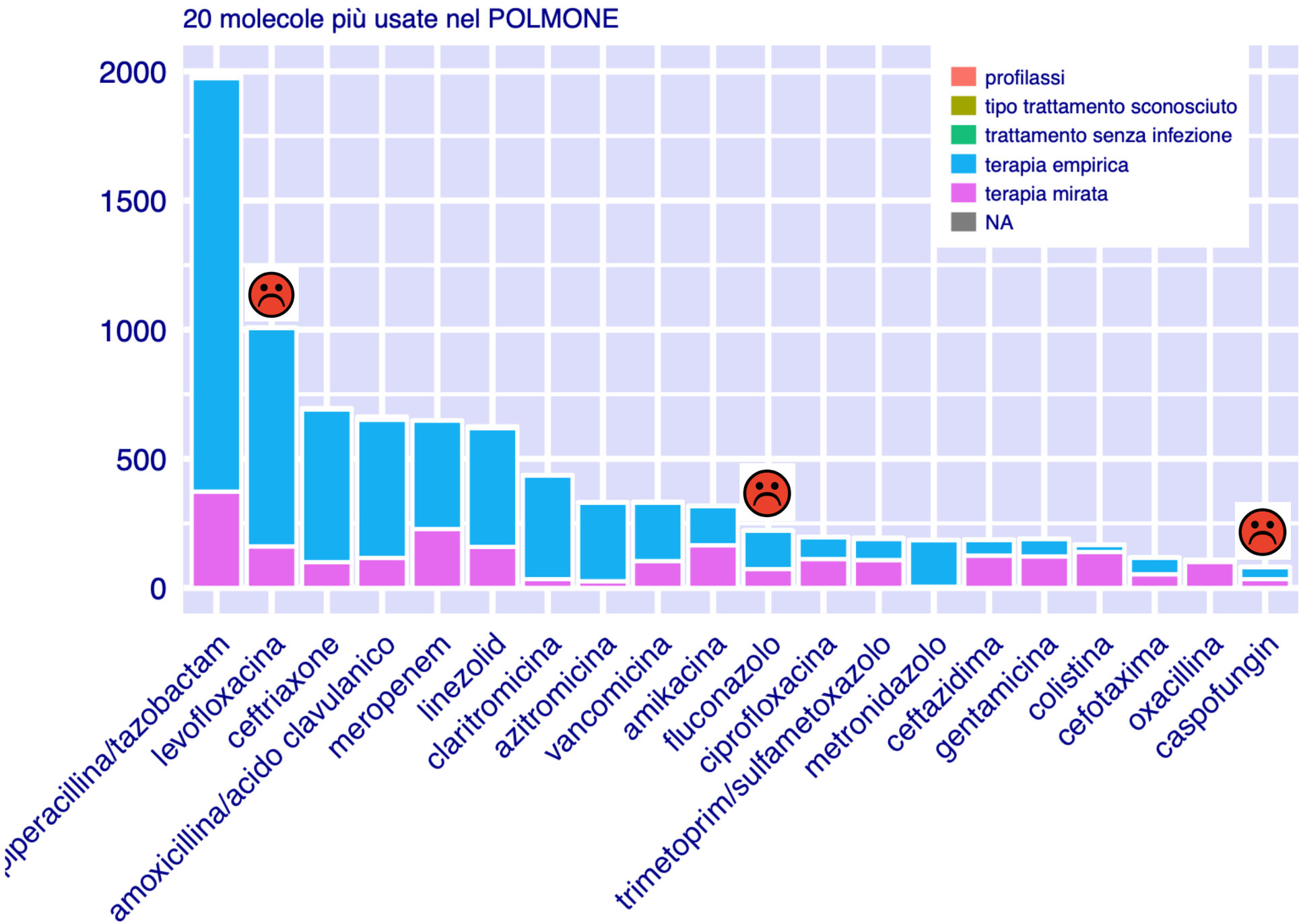
Analisi per sede

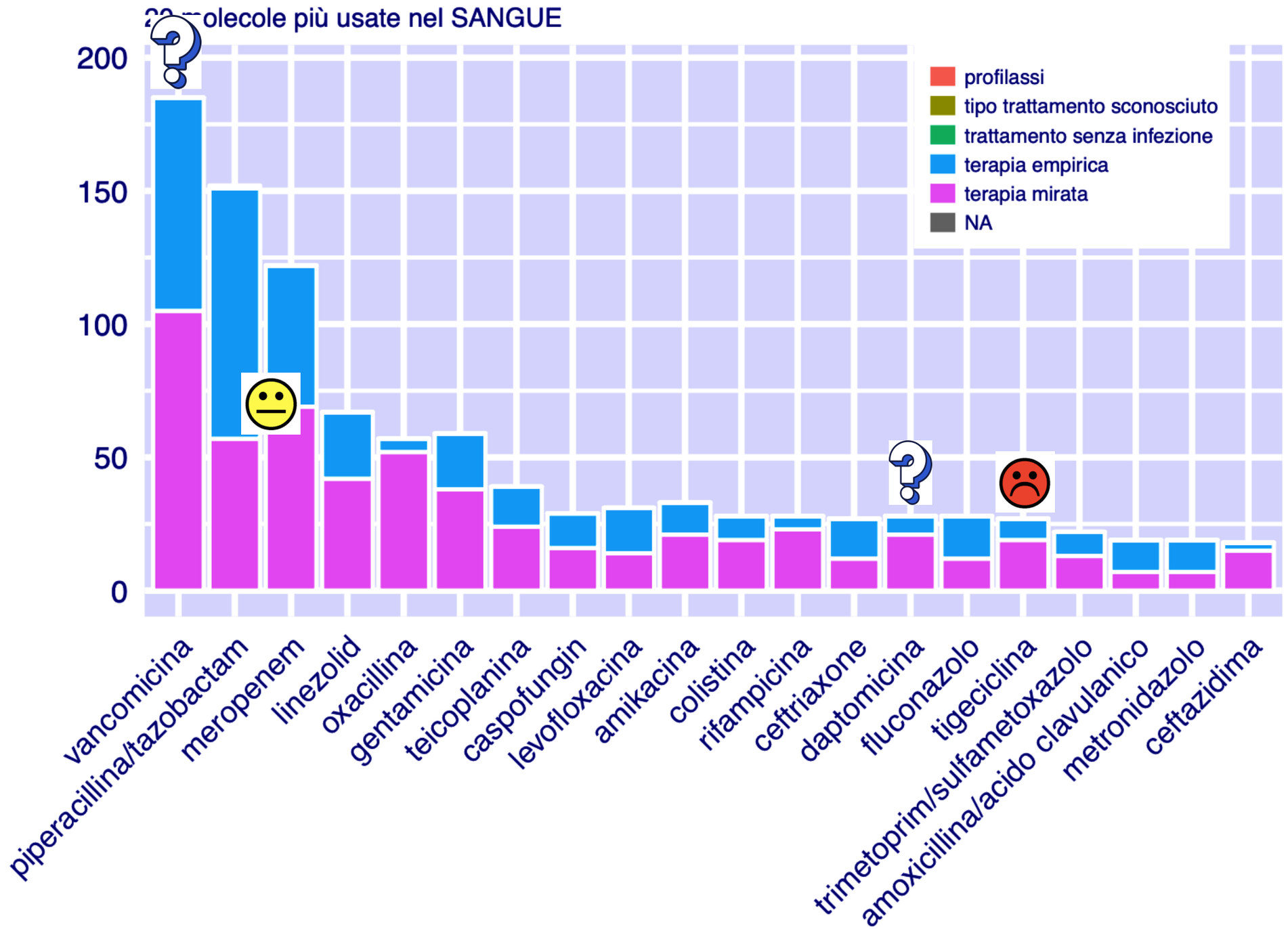


Analisi per sede

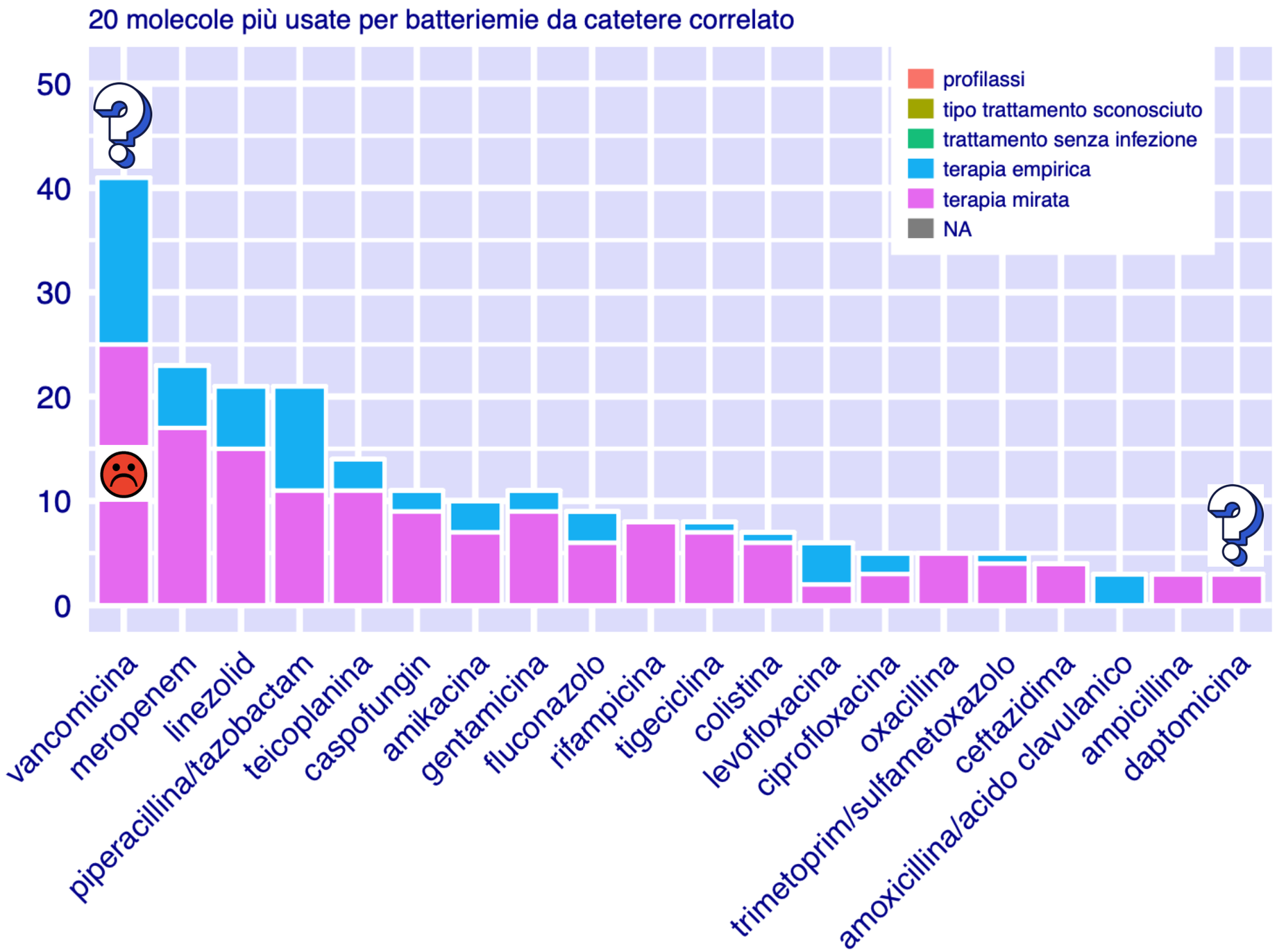
	pazienti	profilassi	terapia		nessuno	sconosciuto	no infezione
			empirica	mirata			
piperacillina/tazobactam	1812	0	1601	373	0	0	1
levofloxacina	969	0	846	161	0	0	0
ceftriaxone	668	0	591	100	0	0	1
amoxicillina/acido clavulanico	610	0	535	116	0	0	1
meropenem	607	0	420	228	0	0	0
linezolid	593	0	461	159	0	0	0
claritromicina	424	0	403	34	0	0	0
azitromicina	320	0	304	26	0	0	0
vancomicina	314	0	227	104	0	0	0
amikacina	299	0	152	165	0	0	0
fluconazolo	217	0	149	73	0	0	0
ciprofloxacina	196	0	85	112	0	0	1
trimetoprim/sulfametoxazolo	187	0	83	108	0	0	0
metronidazolo	184	0	180	5	0	0	0
ceftazidima	179	0	62	125	0	0	0
gentamicina	179	0	69	122	0	0	0
colistina	159	0	29	139	0	0	0
cefotaxima	112	0	65	53	0	0	0
oxacillina	106	0	8	101	0	0	0
caspofungin	78	0	47	34	0	0	0

Tabella A.1.1: Numero di pazienti infetti al POLMONE per tipologia di trattamento e molecola relativi a Figura 1.1. Ogni paziente può ricevere più di un tipo di trattamento con la stessa molecola.

Analisi per sede



Analisi per sede



Analisi per sede

	pazienti	profilassi	terapia		nessuno	sconosciuto	no infezione
			empirica	mirata			
vancomicina	38	0	16	25	0	0	0
meropenem	23	0	6	17	0	0	0
linezolid	19	0	6	15	0	0	0
piperacillina/tazobactam	19	0	10	11	0	0	0
teicoplanina	12	0	3	11	0	0	0
caspofungin	11	0	2	9	0	0	0
amikacina	10	0	3	7	0	0	0
gentamicina	10	0	2	9	0	0	0
fluconazolo	8	0	3	6	0	0	0
rifampicina	8	0	0	8	0	0	0
tigeciclina	8	0	1	7	0	0	0
colistina	7	0	1	6	0	0	0
levofloxacina	6	0	4	2	0	0	0
ciprofloxacina	5	0	2	3	0	0	0
oxacillina	5	0	0	5	0	0	0
trimetoprim/sulfametoxazolo	5	0	1	4	0	0	0
ceftazidima	4	0	0	4	0	0	0
amoxicillina/acido clavulanico	3	0	3	0	0	0	0
ampicillina	3	0	0	3	0	0	0
daptomicina	3	0	0	3	0	0	0

Tabella A.1.3: Numero di pazienti con BATTERIEMIA DA CATETERE VASCOLARE per tipologia di trattamento e molecola relativi a Figura 1.3. Ogni paziente può ricevere più di un tipo di trattamento con la stessa molecola.

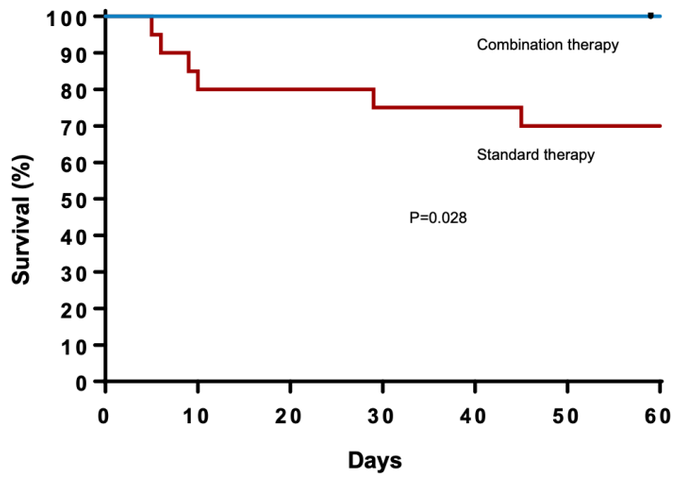
Clinical Data on Daptomycin plus Ceftaroline versus Standard of Care Monotherapy in the Treatment of MRSA Bacteremia

Geriak M et al Antimicrob Agents Chemother May 2019

BACKGROUND**: Vancomycin (VAN) and daptomycin (DAP) are approved as a monotherapy for methicillin-resistant Staphylococcus aureus (MRSA) bacteremia. A regimen of daptomycin plus ceftaroline (DAPCPT* **17 ptz)** *has shown promise in published case series of MRSA salvage therapy, but no comparative data exist to compare up-front DAPCPT head-to- head therapy versus standard monotherapy (23 ptz***) as an initial treatment.*

TABLE 4 Study outcomes

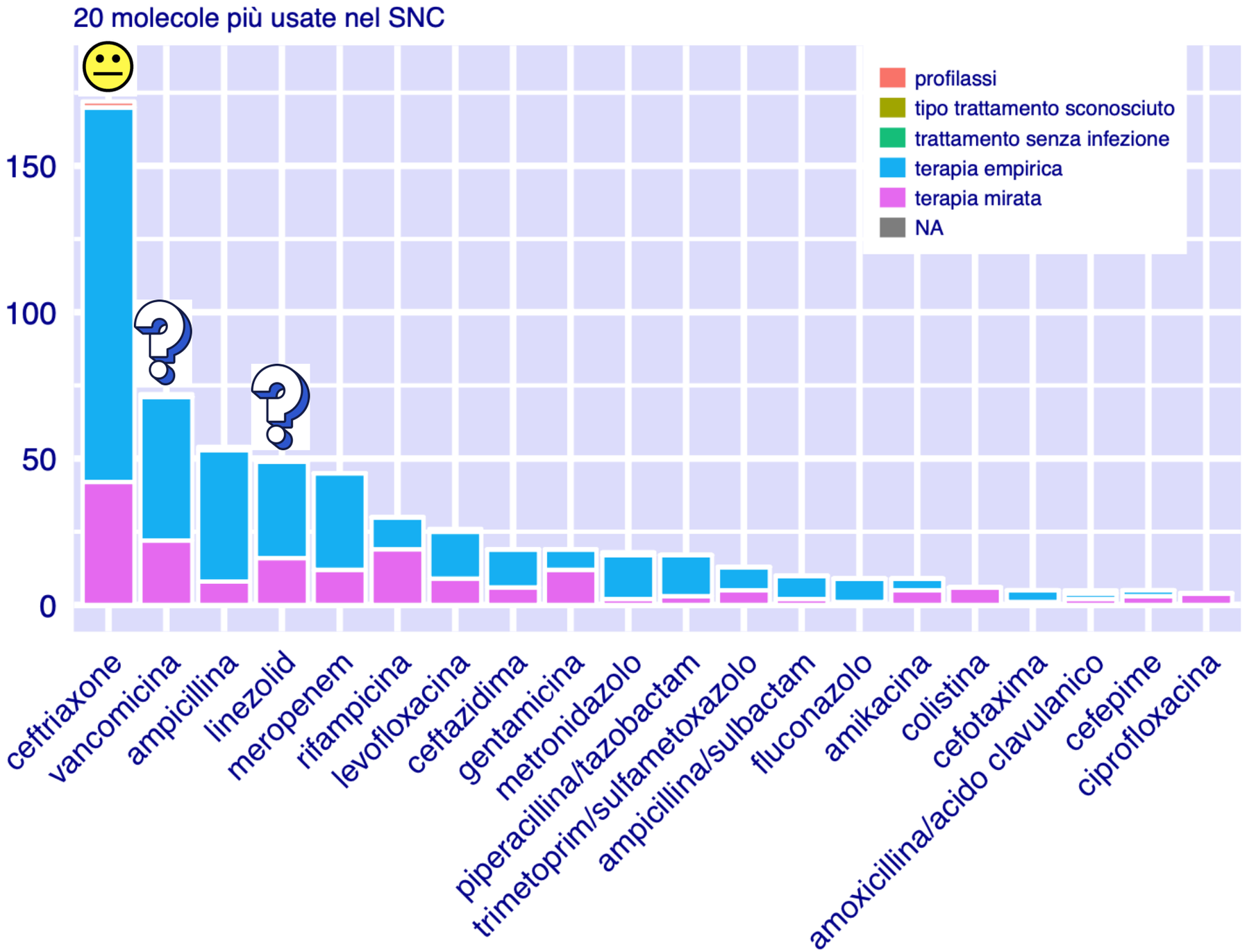
Outcome	Values by treatment type: Combination therapy	Monotherapy	*P* value
Mortality, *n* (%)			
In hospital	0 (0)	6 (26)	0.02
30 day	0 (0)	6 (26)	0.02
90 day	0 (0)	7 (30)	0.03
Bacteremia duration, median (IQR) days	3 (1.5, 5.5)	3 (1, 5.3)	0.56
Length of stay, median (IQR) days	11 (6, 14)	12 (8, 23)	0.24



Among patients with an IL-10 concentration of 5 pg/ml, ***0%*** *(0/14) died in the DAPCPT group versus* ***26%*** *(5/19) in the monotherapy group (****P 0.057****)*

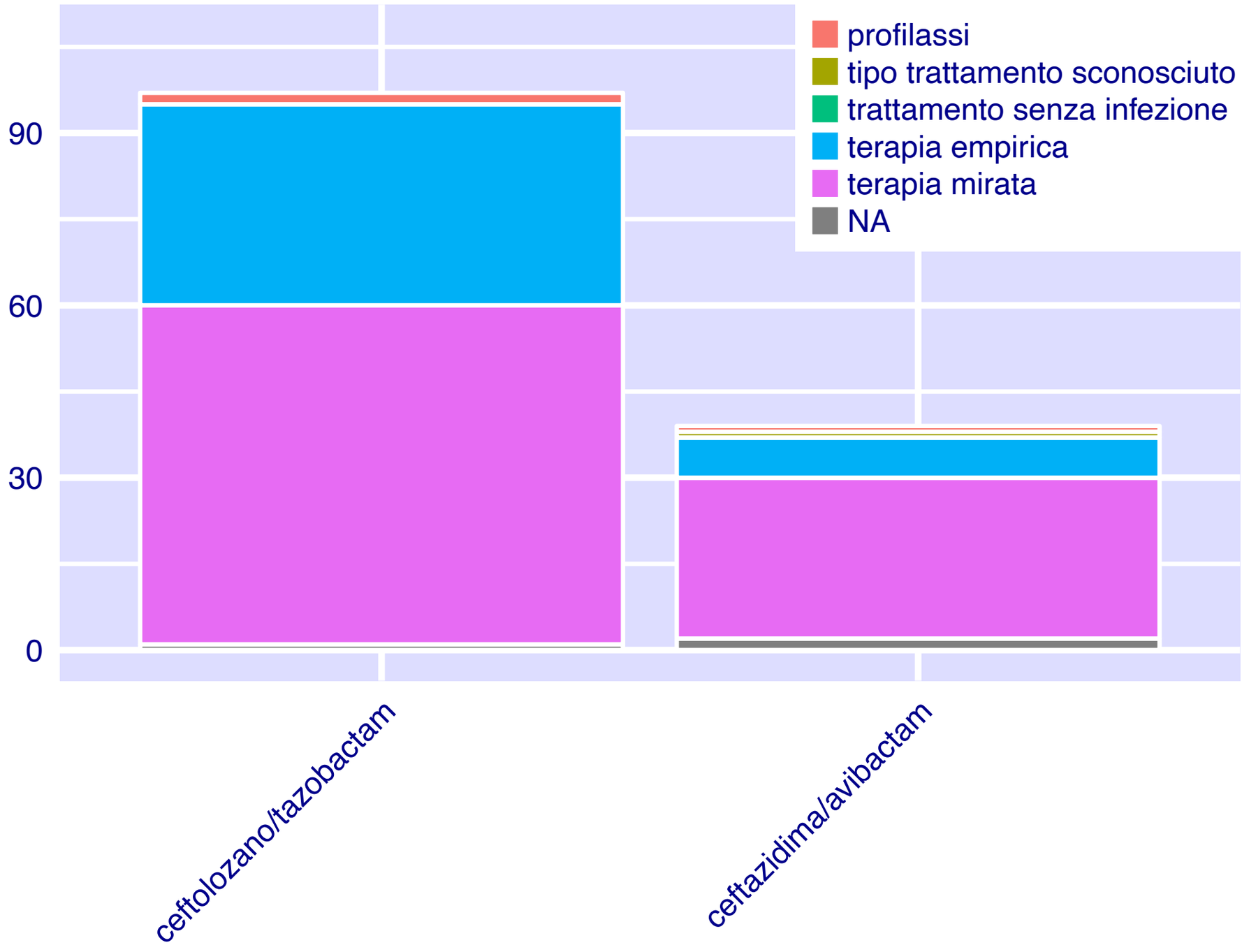
The survival benefit, if any, may be limited to patients with high-risk endovascular sources and those with IL-10 of 5 pg/ml on the day of first positive blood culture.

Analisi per sede

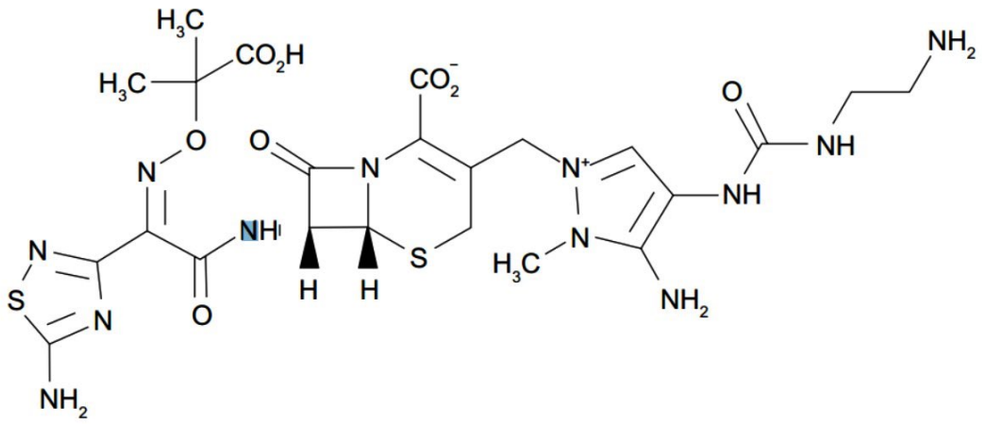


Nuove molecole

DAL 2018-01-01 AL 2019-09-10



Changing the b-lactam partner: **Ceftolozane-Tazobactam** and **Ceftazidime-Avibactam**



Activity vs:

- Broad-spectrum β-lactamases and ESBLs of class A (TEM, SHV, CTX-M)
- AmpC-type B-lactamases
- Some class D oxacillinases (OXA-1)

No/poor activity vs:

- Carbapenemases (MBLs, KPC, OXA)
- OXA-type β-lactamases

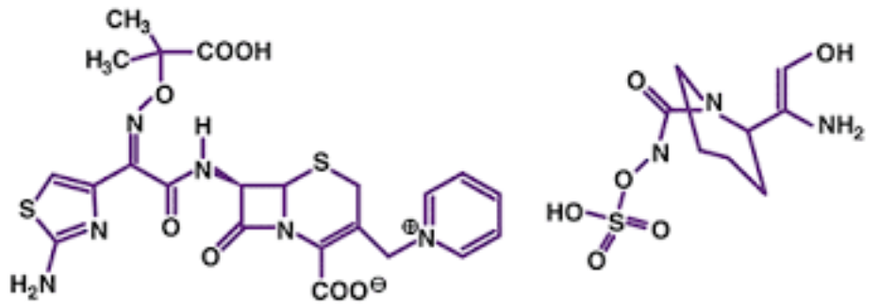


Figure 2. Ceftazidime-Avibactam (Avycaz)

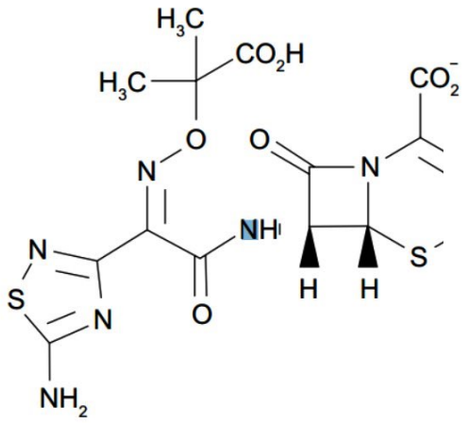
Activity vs:

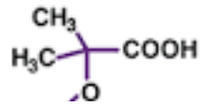
- Broad-spectrum β-lactamases and ESBLs of class A (TEM, SHV, CTX-M)
- AmpC-type B-lactamases
- OXA-48 like
- KPC

No/poor activity vs:

- Carbapenemases (MBLs)

Changing the b-lactam partner: **Ceftolozane-Tazobactam** and **Ceftazidime-Avibactam**





Spettro di azione di **avibactam** vs **vecchi inibitori**

Lagacé-Wiens P et al. Core Evid 2014;9:13

		Clavulanic acid	Tazobactam	Avibactam
Class A	TEM, SHV	✓	✓	✓
	CTX-M	✗	✓	✓
	PER, VEB, GES	✗	✓	✓
	KPC	✗	✗	✓
Class B	**e. g. IMP, VIM, NDM1**	✗	✗	✗
Class C	**Enterics chromos. AmpC**	✗	✗	✓
	***Pseudomonas* chromos. AmpC**	✗	✗	✓
	Plasmid-encoded ACC, DHA, CMY, FOX, LAT, MOX, MIR, ACT	✗	✗	✓
Class D	**Non carbapenemase e. g. OXA-1, -31, -10, -13**	**Variable**	**Variable**	**Variable**
	Carbapenemase e. g. OXA-23, -40, -48, -58	**Variable**	**Variable**	**Variable** OXA-48

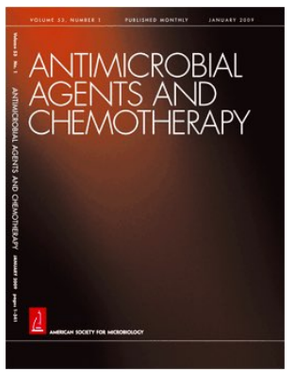
Activity vs:

- Broad-spectrum (TEM, SHV, CTX-
- AmpC-type B-lacta
- Some class D oxa

Ceftolozane: basis for potent anti-Pseudomonas activity

Castanheira et al – AAC 2014

- Stable *vs*. *Pseudomonas* AmpC beta-lactamase
- Entry independent of OprD porin
- Not affected by efflux systems (MexAB, MexXY)



Resistance Mechanisms	Outer Membrane Porin Loss	ß-lactamase Enzyme	Efflux Pump	Efflux Pump
	OprD	AmpC	MexXY	MexAB
Ceftolozane	●	●	●	●
Ceftazidime	●	○	●	○
Cefepime	●	◐	○	○
Piperacillin/tazobactam	●	○	●	○
Imipenem	○	●	●	●
Meropenem	◐	●	○	◐

● Not affected ◐ Partially affected ○ Affected

Ceftolozane: basis for potent anti-Pseudomonas activity

Castanheira et al – AAC 2014

- Stable *vs*
- Entry ind
- Not affec

PBP	IC_{50} (mg/L) ± SD		
	Ceftolozane	Ceftazidime	Imipenem
1b	0.07 ± 0.01	0.12 ± 0.03	0.13 ± 0.01
1c	0.64 ± 0.17	>2	0.08 ± 0.005
2	1.36 ± 0.56	>2	0.08 ± 0.01
3	0.02 ± 0.007	0.04 ± 0.01	0.12 ± 0.2
4	0.29 ± 0.05	1.23 ± 0.49	0.02 ± 0.01
5/6	>2	>2	0.2 ± 0.09
MIC (mg/L) for strain PAO1	0.5	1	1

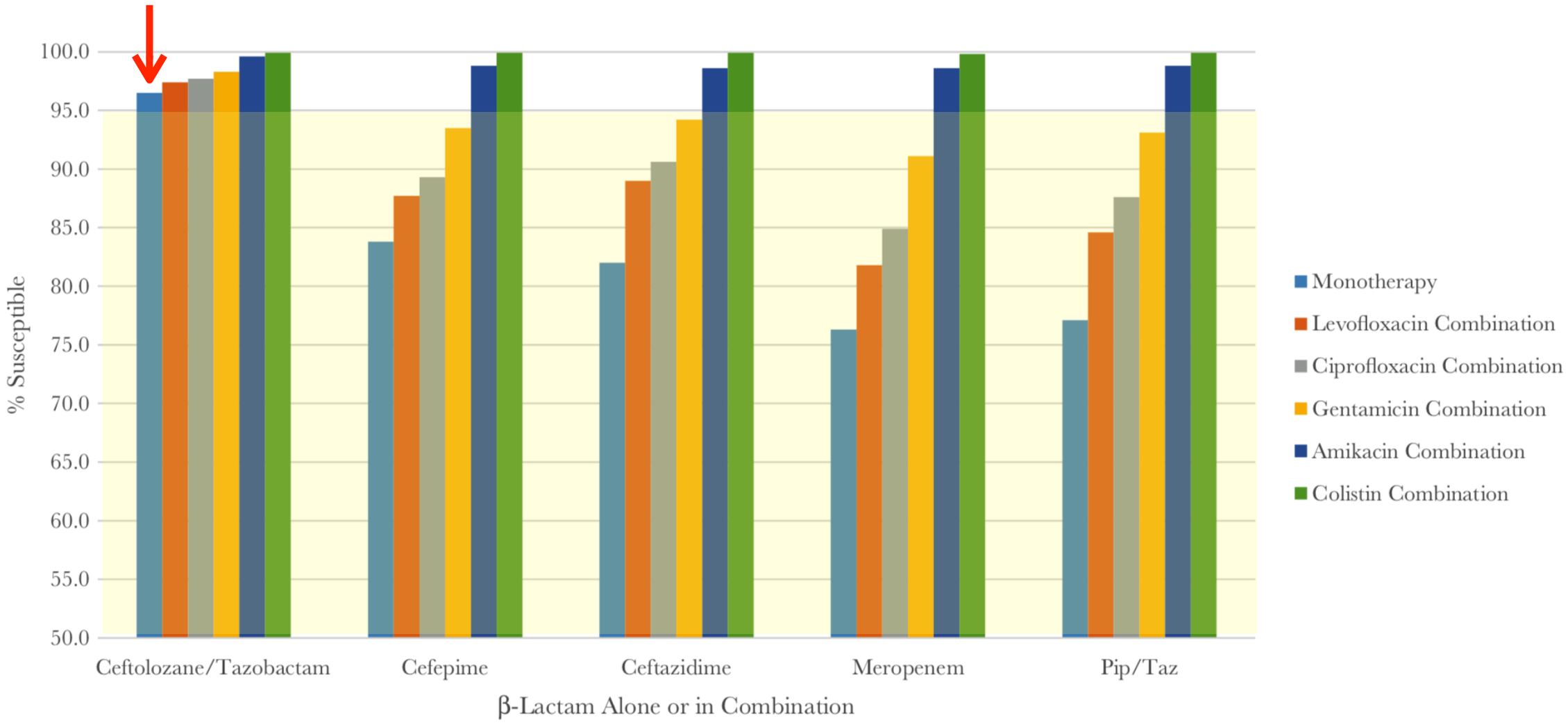
Resistance Mecha				
Ceftolozane				
Ceftazidime				
Cefepime				
Piperacillin/tazob				
Imipenem	○	●	●	●
Meropenem	◐	●	○	◐

● Not affected ◐ Partially affected ○ Affected

Ceftolozane-Tazobactam Monotherapy

Comparison of the in Vitro Susceptibility of TOL-TAZ with the Cumulative susceptibility Rates of Standard Antibiotic combinations when tested against Pseudomonas aeruginosa from ICU patients with BSIs or Pneumonia

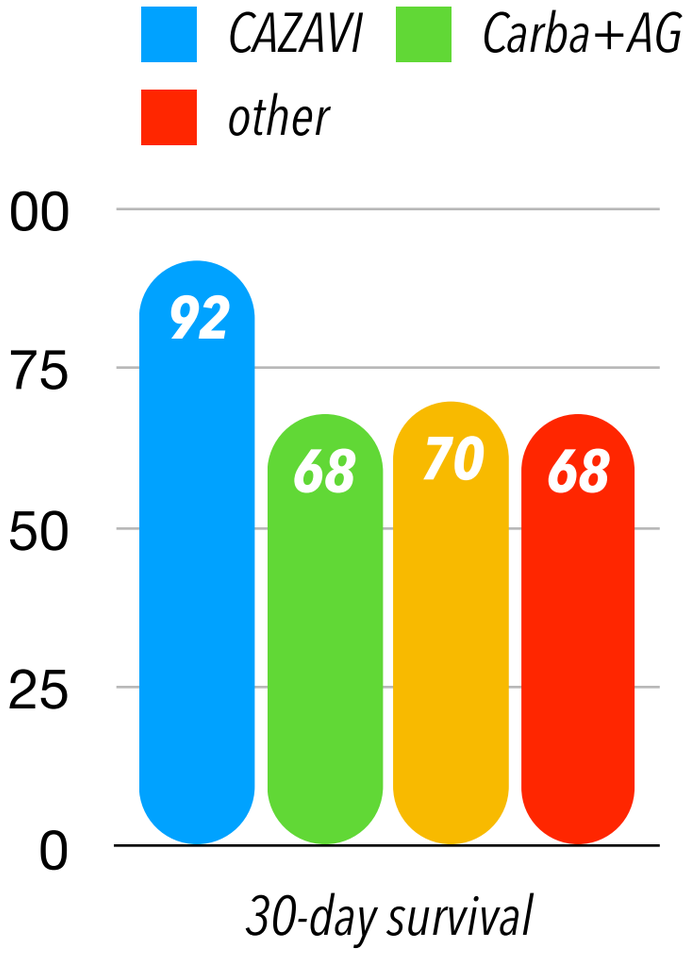
Methods: *Isolates were collected from intensive care unit patients hospitalized in 32 US hospitals from 2011 to 2017. The susceptibilities of 1543 P. aeruginosa isolates from bloodstream infections (198 isolates,* ***12.8%****) or pneumonia (1345 isolates,* ***87.2%****) were determined for ceftolozane-tazobactam and comparators*

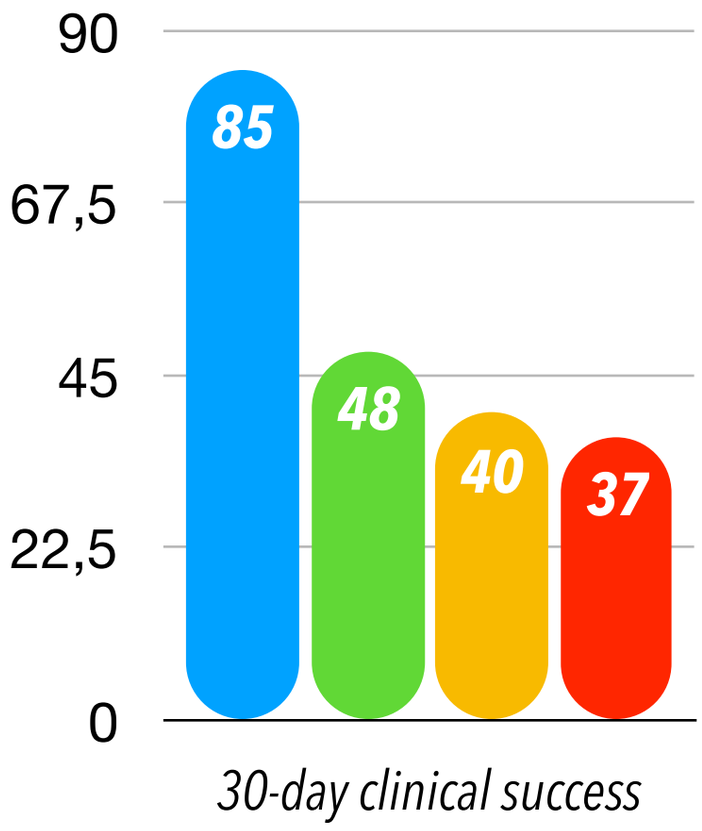


A threshold of 95% susceptibility was used for comparison as recommended in the IDSA guidelines for management of patients with HAP/VAP

Ceftazidime-Avibactam is Superior to Other Treatment Regimens against Carbapenem-Resistant Klebsiella pneumoniae Bacteremia

Shields RK et al. Antimicrob Agents Chemother 2017;61(8):e00883-17





a retrospective study

CAZ-AVI: meccanismi di resistenza acquisita

- **Mutazioni KPC**
  - D179Y (perdita di attività su carbapenemi, pip/taz e aztreonam)
  - T243M (perdita di attività su carbapenemi e pip/taz)
  - 165EL166 (perdita di attività su carbapenemi, pip/taz e aztreonam)
  - V240G (ridotta attività su meropenem)

- **Mutazioni in OmpK36**
  - T333N
  - Inattivazione inserzionale (IS*5*)

- **Aumentata espressione di KPC**
  - aumento del numero di copie plasmidiche

Antibiotico	MIC mg/L (S/I/R)
Amoxi/Clav	>64 R
Pip/Tazo	>256 R
Ceftazidime	>64 R
Ertapenem	>2 R
Imipenem	0.5 S
Meropenem	2 S
Ceftazidime/Avibactam	>16 R
Amikacina	32 R
Gentamicina	1 S
Ciprofloxacina	>2 R
Tigeciclina	0.5 S
Colistina	0.5 S

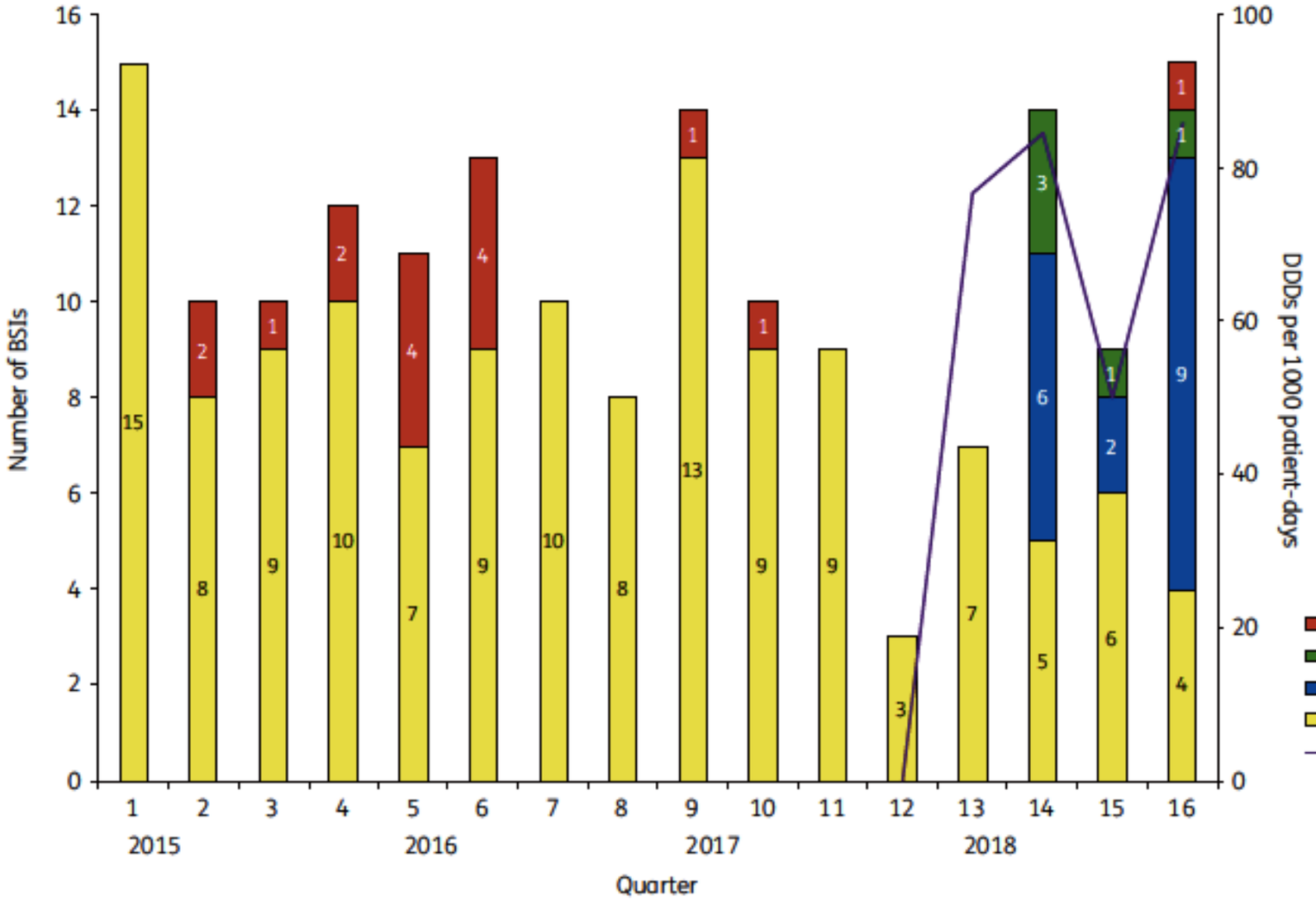
Haidar et al – AAC 2017
Compain & **Arthur** – AAC 2017
Shields et al – AAC 2017
Humphries & **Hamarajata** AAC 2017
Shields et al – OFID 2017

Cortesia Dr Giani

Reversal of carbapenemase-producing Klebsiella pneumoniae epidemiology from bla$_{KPC}$- to bla$_{VIM}$-harbouring isolates in a Greek ICU after introduction of ceftazidime/avibactam

Papadimitriou-Olivgeris M J Antimicrob Chemother jul 2019

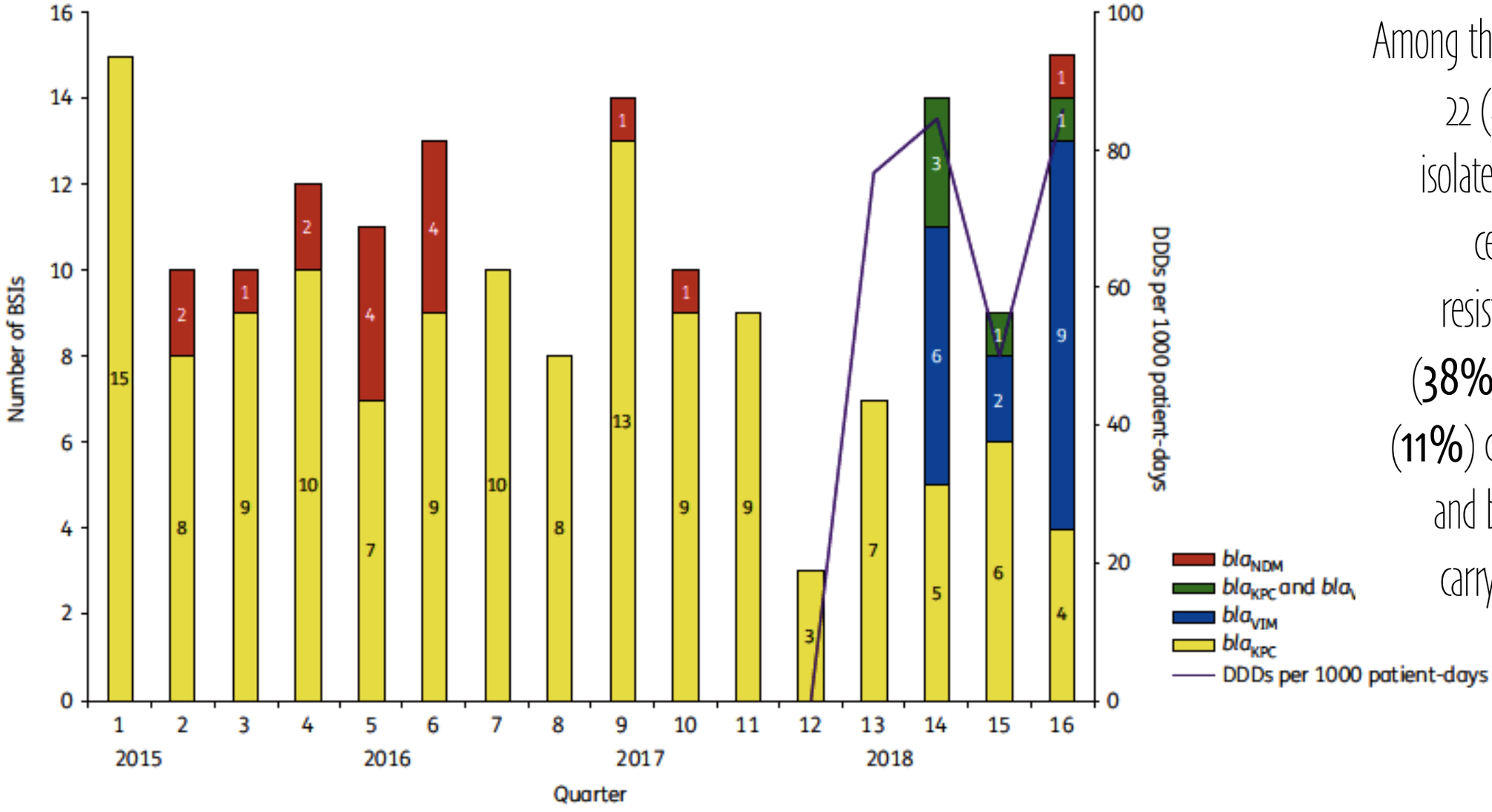
From 2015 to 2017 (**125 BSIs**), KPC-producing strains (110; **88%**) predominated, followed by NDM-producing strains (15; **12%**), whereas no VIM-producing strain was isolated.



Among the **45 BSIs** in 2018, 22 (**49%**) were due to isolates carrying blaKPC (4 ceftazidime/avibactam resistant), followed by 17 (**38%**) carrying blaVIM, 5 (**11%**) carrying both blaKPC and blaVIM, and 1 isolate carrying blaNDM (**2%**).

The results of our study highlight the need **to optimize the appropriate** and **judicious use** of ceftazidime/avibactam to minimize the consequences associated with antibiotic-resistant organisms

From 2015 to 2017 (**125 BSIs**), KPC-producing strains (110; **88%**) predominated, followed by NDM-producing strains (15; **12%**), whereas no VIM-producing strain was isolated.



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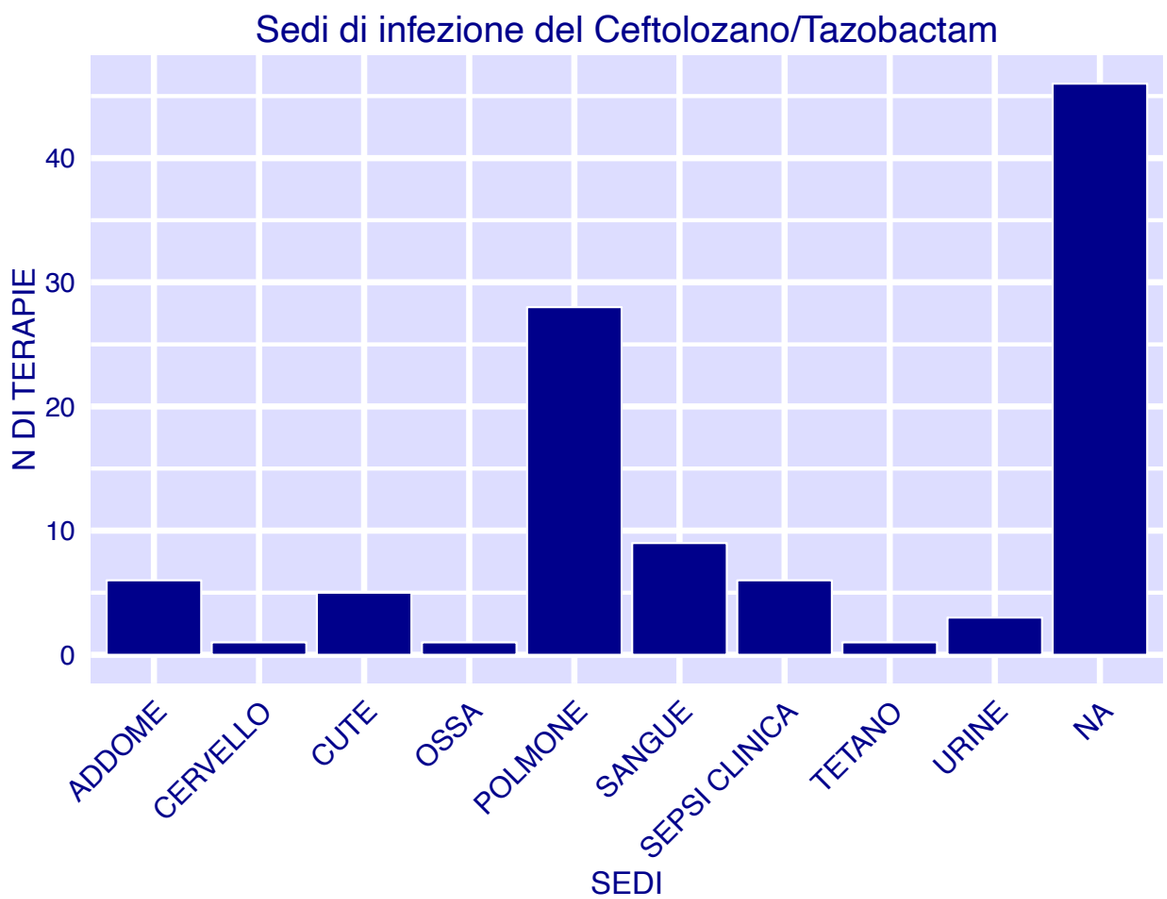
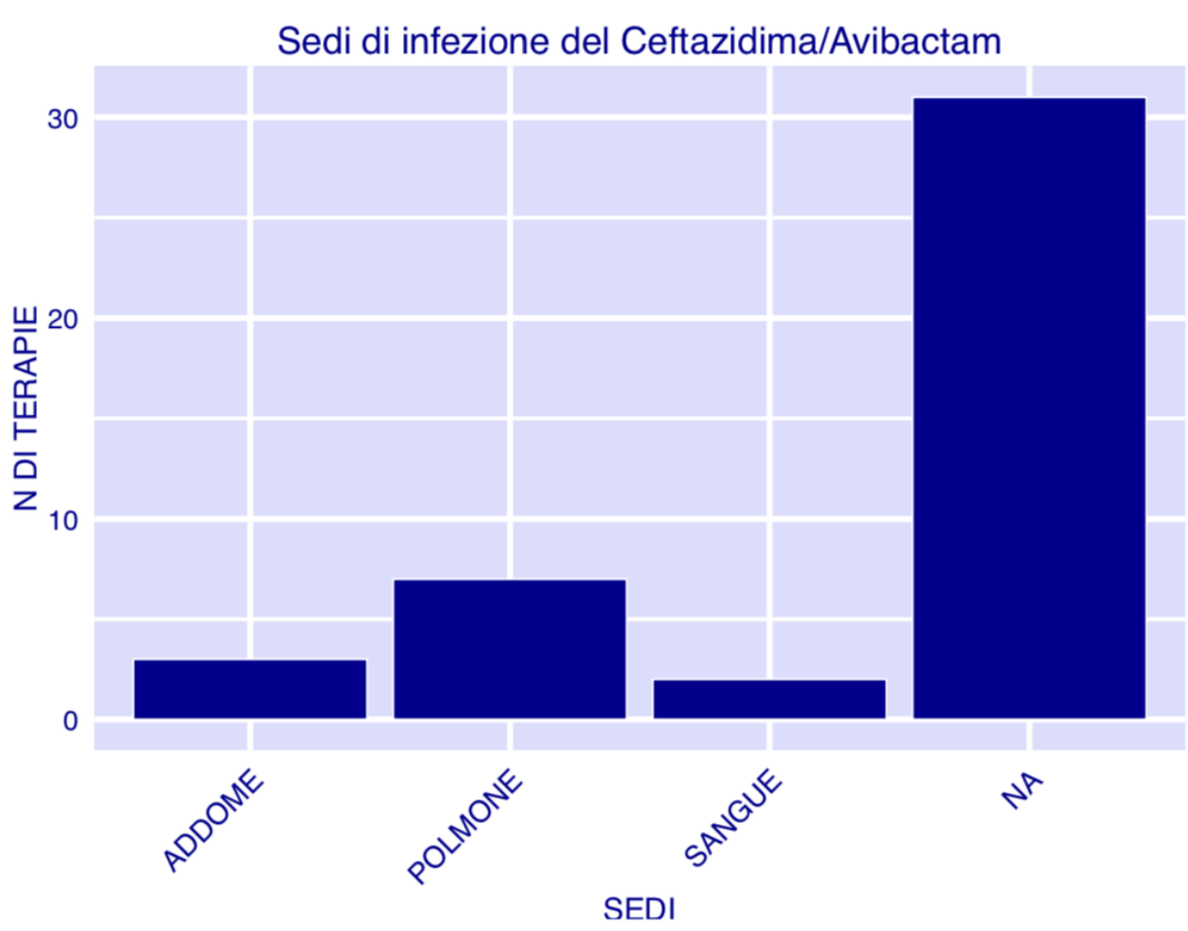
Nuove molecole

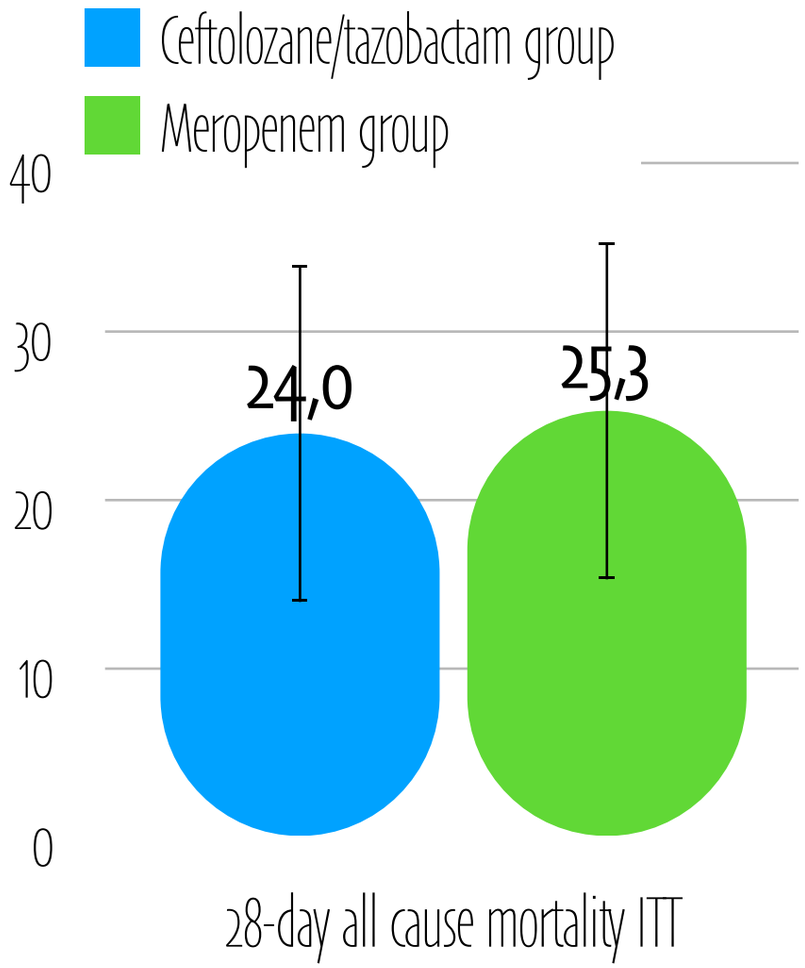
Numero di profilassi o terapie antibiotiche di **ceftolozano/tazobactam** e **ceftazidime/avibactam** suddivise per le diversi sedi dell'infezione

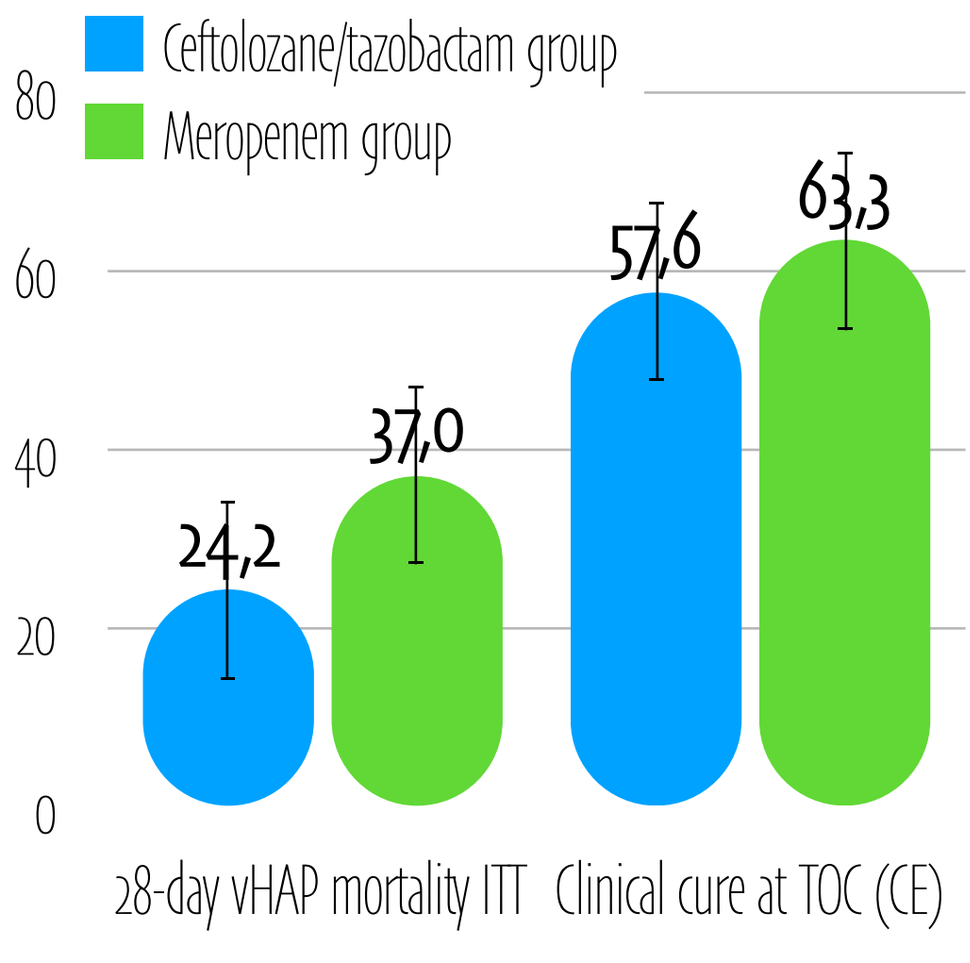




Ceftolozane-Tazobactam versus Meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double.blind, phase 3, non-inferiority trial

Kollef MH Lancet Infect Dis online Sep 25,2019





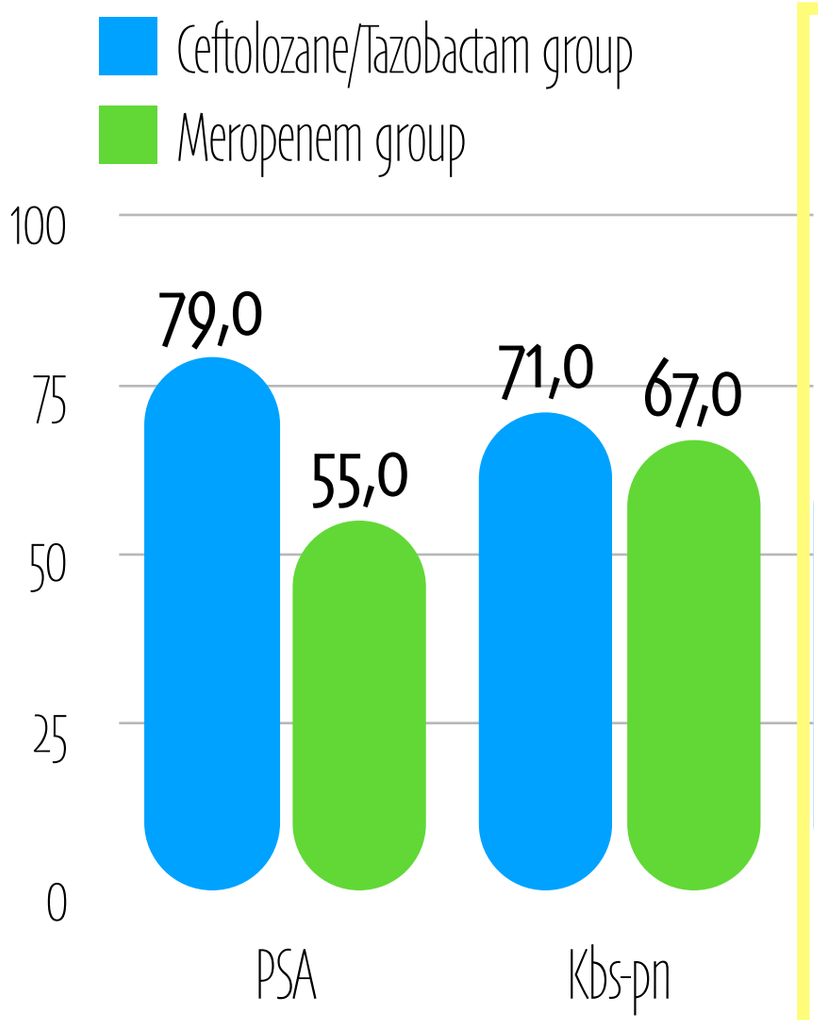
vHAP ventilated hospital-acquired pneumonia

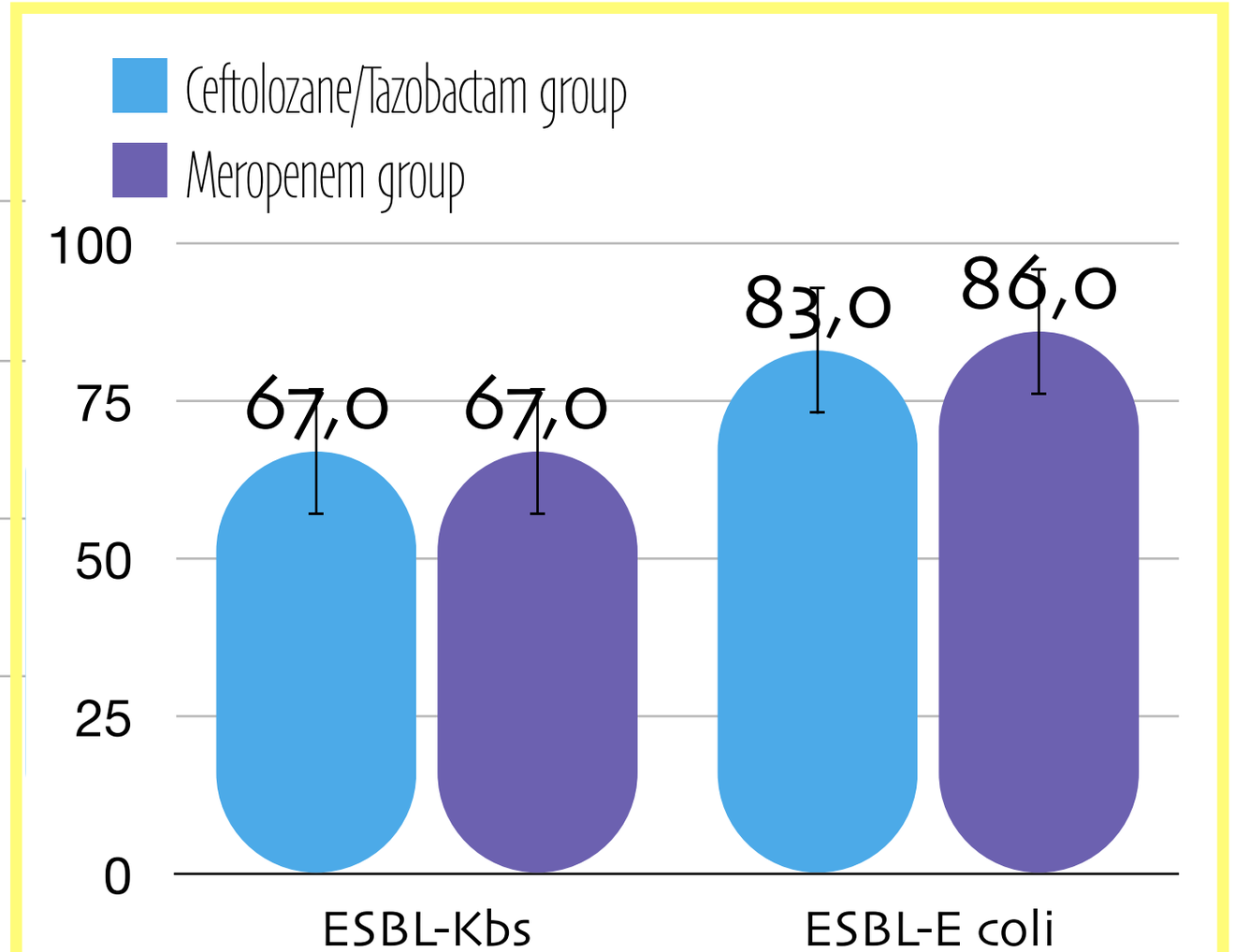
Ceftolozane-Tazobactam versus Meropenem for treatment of nosocomial pneumonia (ASPECT-NP): a randomised, controlled, double.blind, phase 3, non-inferiority trial

Kollef MH Lancet Infect Dis online Sep 25,2019

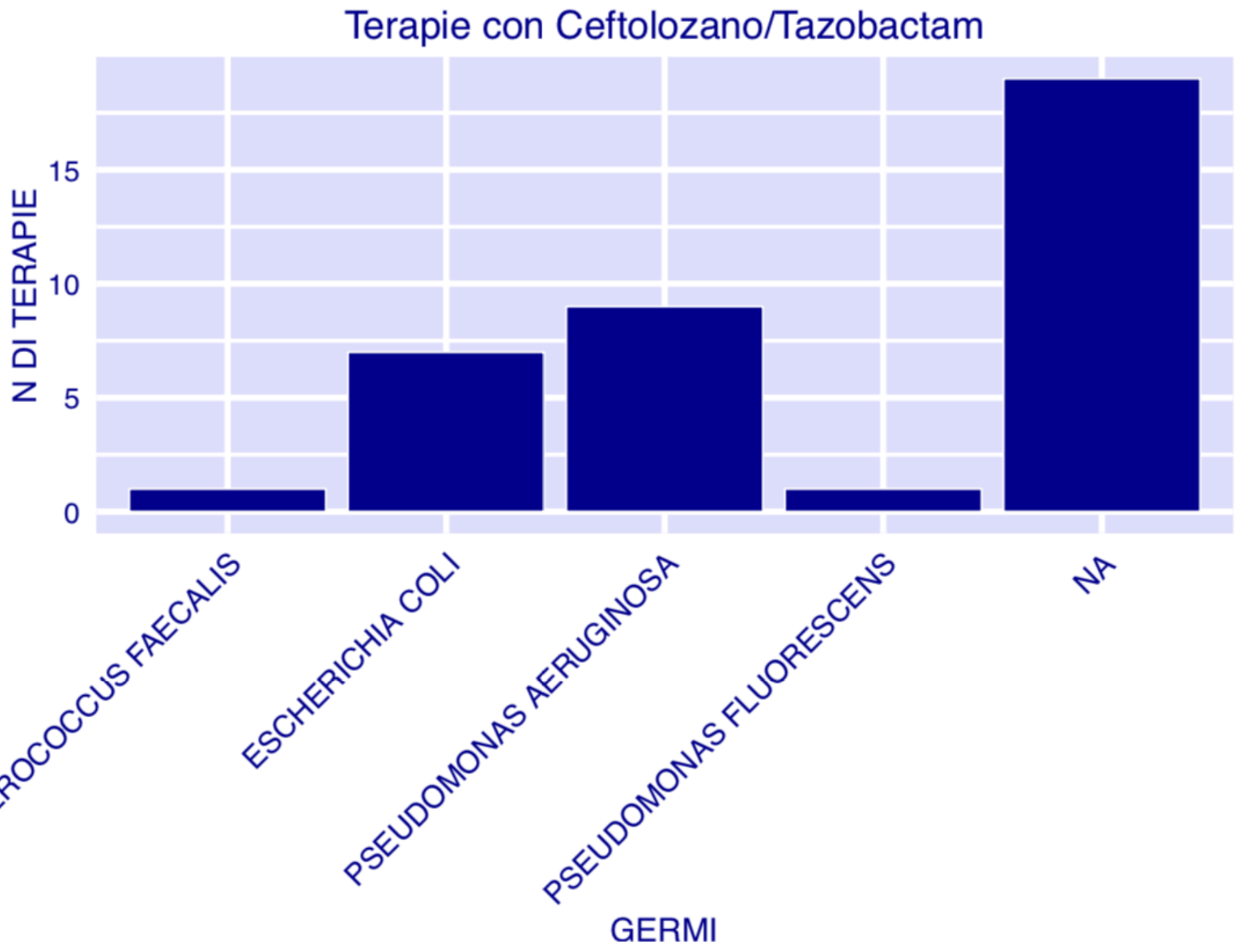
Martin-Loeches I ECCMID 2019 poster O0302

Microbiologic eradication

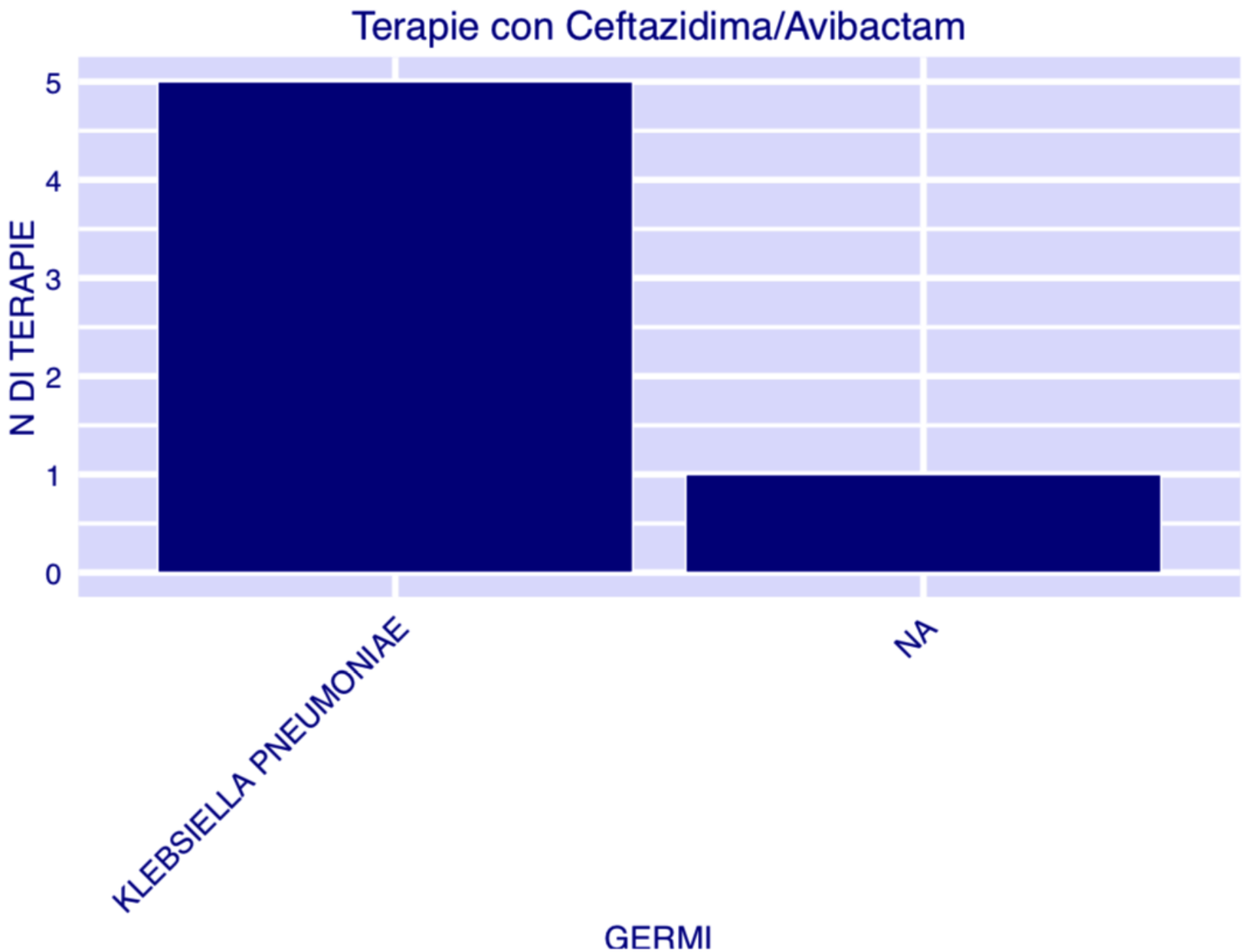




Nuove molecole



Nuove molecole



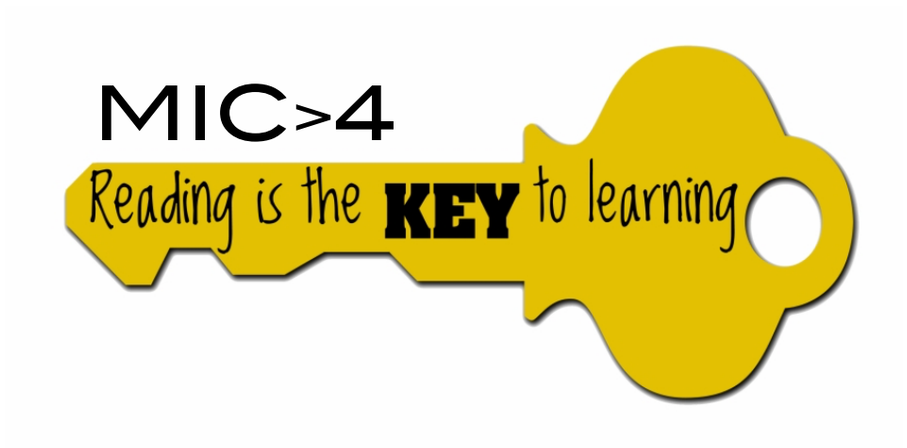
Rationalizing antimicrobial therapy in the ICU: a narrative review

Timsit JF et al Intensive Care Med 2019

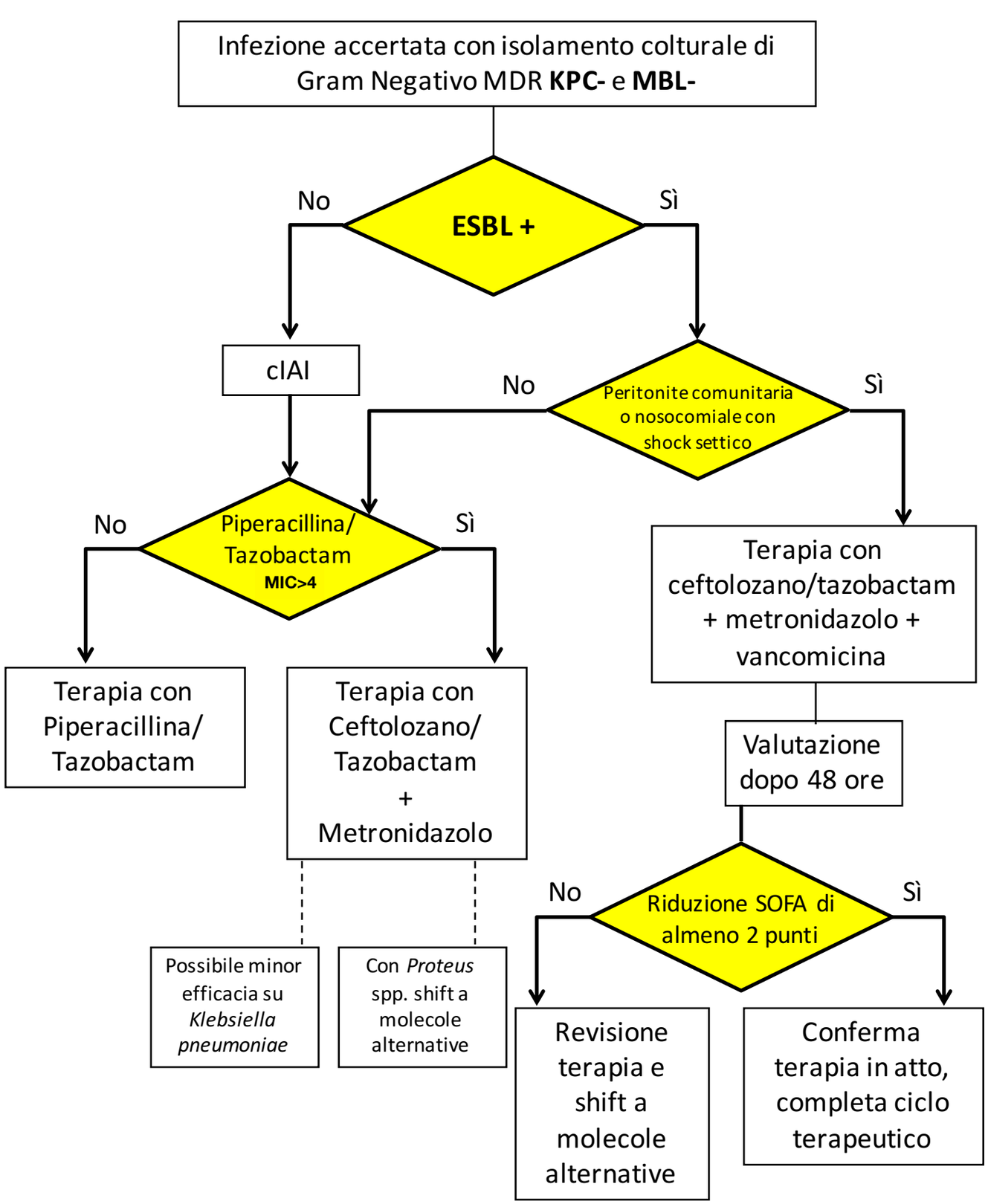
29th ECCMID Amsterdam, Netherlands 13–16 April 2019 | ESCMID

- Outcome della piperacillina/tazobactam sembra dipende dalla MIC; < 4 mg/L miglior ctions in outcome nello studio Merino

- Pip/Tazo utile nella terapia mirata specie se MIC basse



Protocollo CARBAPENEM-SPARING in area critica nel paziente con cIAI: scelta ragionata



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