NOVEL DATA ON NEW AND OLD EPIDEMICS

CONFERENCE

Milan, 12 September 2023

Starhotels E.c.ho. Milano

UNIVERSITÀ DEGLI STUDI DI MILANO

Sistema Socio Sanitario
Regione Lombardia
ASST Santi Paolo e Carlo

Massimo Puoti

University Milano Bicocca
School of Medicine and Surgery

SC Malattie Infettive

ASST Grande Ospedale Metropolitano Niguarda

Place in therapy of new antibiotics, from new molecules to long acting strategies

SCHOOL OF MEDICINE AND SURGERY

COI

- Speaker in own events o membro di advisory board temporanei o percettore di travel grants negli ultimi 2 anni
  - Merck
  - Abbvie
  - Gilead
  - ViiV
  - Menarini
  - Shionogi
  - Pfizer
  - Angelini
  - Infectopharm

Place in therapy of new antibiotics from new molecules to long acting strategies

- New drugs for MDR G-
  - Ceftazidime/avibactam
  - Ceftolozano/tazobactam
  - Cefiderocol
  - Meropenem/vaborbactam
  - Imipenem/relebactam

- Long acting strategies for G+
  - Dalbavancin
  - Oritavancin

Place in therapy of new antibiotics from new molecules to long acting strategies

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Clinical Microbiology and Infection

Guidelines

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine)

Potential *in vitro* activity of antibiotics against target carbapenem-resistant Gram-negative bacteria

	CRAB	ESBLs	CRPA non-MBL	CRE non-CP	CRE-KPC	CRE-OXA-48	CRE-MBL
New antibiotics							
Ceftolozane- tazobactam	No	Yes	Yes	No	No	No	No
Ceftazidime-avibactam	No	Yes	Yes	+/-	Yes	Yes	No
Meropenem-vaborbactam	No	Yes	No	+/-	Yes	No	No
Imipenem-cilastatin/ relebactam	No	Yes	Yes	+/-	Yes	No	No
Cefiderocol	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Old antibiotics							
Polymyxins	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Aminoglycosides	+/-	+/-	+/-	+/-	+/-	+/-	+/-
Fosfomycin iv	No	Yes	+/-	+/-	+/-	+/-	+/-
Aztreonam	No	No	+/-	No	No	No	+/-
Tigecycline	Yes	Yes	No	Yes	Yes	Yes	Yes
Temocillin	No	Yes	No	No	+/-	No	No

CRAB, carbapenem-resistant Acinetobacter baumannii; CRE non-CP, non-carbapenemase-producing carbapenem-resistant Enterobacterales; CRPA non-MBL, carbapenem-resistant Pseudomonas aeruginosa non-metallo-b-lactamase-producing; ESBLs, extended-spectrum b-lactmases;; MBL, metallo-b-lactamase;

Approved indications for antibiotics active against target carbapenem-resistant Gram-negative bacteria

	cUTI	cIAI	cSSTI	HAP & VAP	Gram negative infections with limited treatment options
New antibiotics					
Ceftolozane- tazobactam	Yes	Yes	No	Yes	No
Ceftazidime-avibactam	Yes	Yes		Yes	Yes (EMA)
Meropenem-vaborbactam	Yes	No	No	YES (EMA)	Yes (EMA)
Imipenem-cilastatin/ relebactam	Yes (FDA)	Yes (FDA)	No	Yes (EMA)	Yes (EMA)
Cefiderocol	Yes (FDA)	No	No	Yes (FDA)	Yes (EMA)
Old antibiotics					
Polymyxins	No	No	No	No	Yes
Fosfomycin iv	No	No	No	No	Yes (FDA)
Aztreonam	No	No	No	No	Yes
Tigecycline	No	Yes	Yes	No	No
Temocillin	No	No	No	No	Orphan drug status for the treatment of Burkholderia cepacia infections in cystic fibrosis

CRAB, carbapenem-resistant Acinetobacter baumannii; CRE non-CP, non-carbapenemase-producing carbapenem-resistant Enterobacterales; CRPA non-MBL, carbapenem-resistant Pseudomonas aeruginosa non-metallo-b-lactamase-producing; ESBLs, extended-spectrum b-lactmases;; MBL, metallo-b-lactamase;

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Guidelines

European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines for the treatment of infections caused by multidrug-resistant Gram-negative bacilli (endorsed by European society of intensive care medicine)

Mical Paul [1, 2, §], Elena Carrara [3, §], Pilar Retamar [4, 5], Thomas Tängdén [6], Roni Bitterman [1, 2], Robert A. Bonomo [7, 8, 9], Jan de Waele [10], George L. Daikos [11], Murat Akova [12], Stephan Harbarth [13], Celine Pulcini [14, 15], José Garnacho-Montero [16], Katja Seme [17], Mario Tumbarello [18], Paul Christoffer Lindemann [19], Sumanth Gandra [20], Yunsong Yu [21, 22, 23], Matteo Bassetti [24, 25], Johan W. Mouton [26, †], Evelina Tacconelli [3, 27, 28, *, §], Jesús Rodríguez-Baño [4, 5, §]

International Journal of Antimicrobial Agents xxx (xxxx) xxx

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Review

Diagnosis and management of infections caused by multidrug-resistant bacteria: guideline endorsed by the Italian Society of Infection and Tropical Diseases (SIMIT), the Italian Society of Anti-Infective Therapy (SITA), the Italian Group for Antimicrobial Stewardship (GISA), the Italian Association of Clinical Microbiologists (AMCLI) and the Italian Society of Microbiology (SIM)

Giusy Tiseo [a,1], Gioconda Brigante [b,1], Daniele Roberto Giacobbe [c,d,1], Alberto Enrico Maraolo [e,1], Floriana Gona [f,1], Marco Falcone [a], Maddalena Giannella [g,h], Paolo Grossi [i], Federico Pea [h,j], Gian Maria Rossolini [k], Maurizio Sanguinetti [l], Mario Sarti [m], Claudio Scarparo [n], Mario Tumbarello [c], Mario Venditti [p], Pierluigi Viale [g,h], Matteo Bassetti [c,d,2], Francesco Luzzaro [q,2], Francesco Menichetti [a,2,*], Stefania Stefani [r,2], Tinelli [s,2]

Enfermedades Infecciosas y Microbiología Clínica 41 (2023) 360–370

Enfermedades Infecciosas y Microbiología Clínica

www.elsevier.es/eimc

Consensus Document

Executive summary of the consensus document of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) on the diagnosis and antimicrobial treatment of infections due to carbapenem-resistant Gram-negative bacteria☆

Vicente Pintado [a,b,*], Patricia Ruiz-Garbajosa [c], David Aguilera-Alonso [d,e], Fernando Baquero-Artigao [f], Germán Bou [g], Rafael Cantón [c], Santiago Grau [h,i,j], Belén Gutiérrez-Gutiérrez [k], Nieves Larrosa [l], Isabel Machuca [m,n], Luis Martínez Martínez [o], María Milagro Montero [i,p], Elena Morte-Romea [q], Antonio Oliver [r], José Ramón Paño-Pardo [q], Luisa Sorlí [i,p]

Last updated March 7, 2022, and posted online at https://www.idsociety.org/practice-guideline/amr-guidance/. Please check website for most updated version of this guidance.

Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and *Pseudomonas aeruginosa* with Difficult-to-Treat Resistance (DTR-*P. aeruginosa*)

Authors

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] & Cornelius J. Clancy[6]

Infectious Diseases Society of America Guidance on the Treatment of AmpC β-lactamase-Producing Enterobacterales, Carbapenem-Resistant *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* Infections

Authors

Pranita D. Tamma,[1] Samuel L. Aitken,[2] Robert A. Bonomo,[3] Amy J. Mathers,[4] David van Duin,[5] & Cornelius J. Clancy[6]

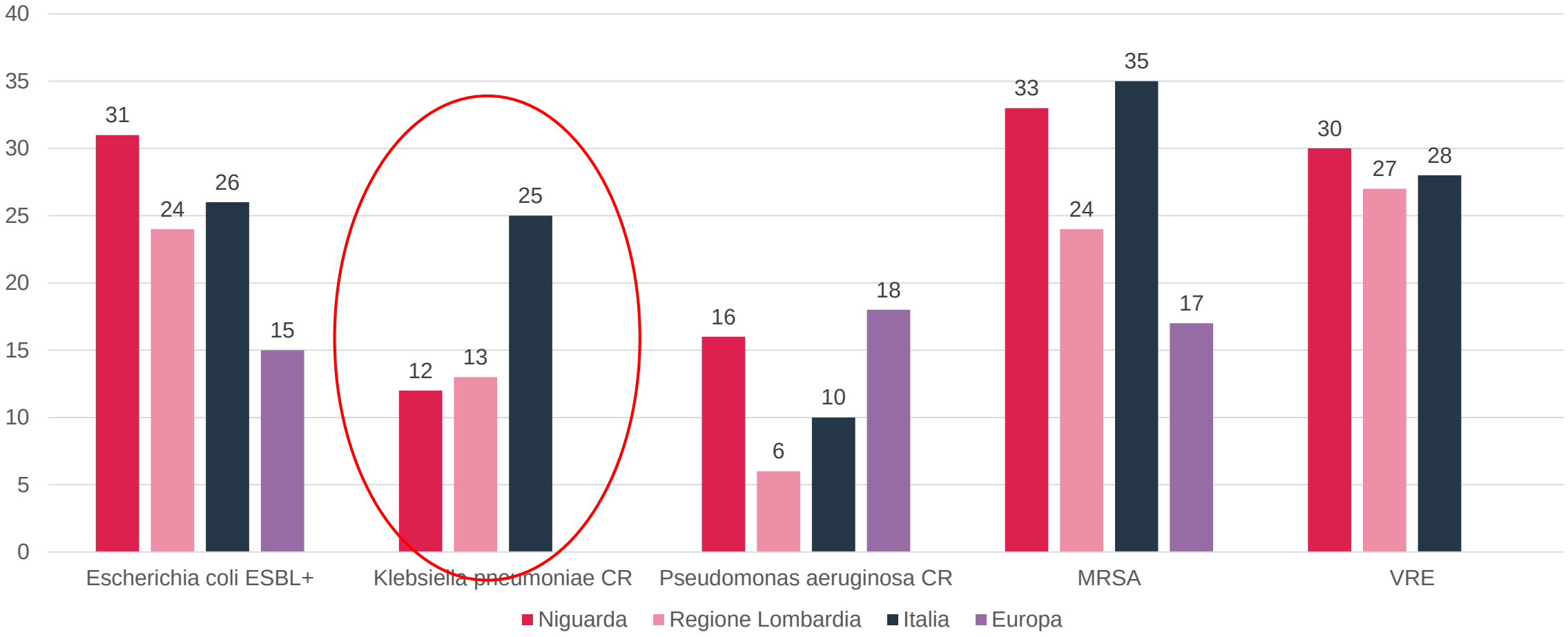
Empiric therapy

- Guided by the
  - most likely pathogens,
  - severity of illness of the patient,
  - likely source of the infection,
  - any additional patient-specific actors (e.g., severe penicillin allergy, chronic kidney disease).
  - Considerations about
    - **previous organisms identified from the patient and associated antibiotic susceptibility data in the last six months**,
    - **antibiotic exposures within the past 30 days**, and
    - **local susceptibility patterns** for the most likely pathogens. Empiric decisions should be refined based on the identity and susceptibility profile of the pathogen.

When should empirical treatment for carbapenem-resistant GNB be considered?

1. Empirical therapy for CR-GNB should be considered in patients with suspected, yet unconfirmed, severe CR-GNB infections (sepsis, septic shock) when the risk of CR-GNB is high enough, or in patients known to be colonized by CR-GNB who develop an infection potentially caused by a GNB. In severely immunocompromised patients (i.e. neutropenic patients and transplant recipients) with systemic, although less severe infections, the same principle applies. Validated CR-GNB infection prognostic scores can assist with therapeutic decision making (**A-II**).
2. The overall rate of carbapemem-resistance among the most epidemiologically relevant GNB at the institution/ward can be used as a surrogate of the risk of CR-GNB. A 10–20% rate of carbapenem-resistance among GNB could be considered as a reasonable threshold to start antimicrobial therapy for CR-GNB in these circumstances (**B-III**).

Isolamenti da emocolture percentuale germi resistenti. Niguarda, Lombardia, Italia, Europa



Regione Lombardia: DG Welfare 8/8/2023 REPORT EMOCOLTURE 2022
Italia: AR – ISS 2021 ; ECDC ITA population weighed 2020 ECDC Europe Population weighed 2020

Dequin *et al. Annals of Intensive Care* (2023) 13:59
https://doi.org/10.1186/s13613-023-01155-4

Annals of Intensive Care

REVIEW Open Access

The place of new antibiotics for Gram-negative bacterial infections in intensive care: report of a consensus conference

Pierre-François Dequin[1,2*], Cécile Aubron[3], Henri Faure[4], Denis Garot[2], Max Guillot[5], Olfa Hamzaoui[6], Virginie Lemiale[7], Julien Maizel[8], Joy Y. Mootien[9], David Osman[10], Marie Simon[11], Arnaud W. Thille[12], Christophe Vinsonneau[13] and Khaldoun Kuteifan[9]

Recommendation 1A These antibiotics should probably not be used empirically in critically ill patients (grade 2-, moderate quality of evidence, strong agreement)

Recommendation 1B The panel suggests that the use of these antibiotics should only be considered in the exceptional case of septic shock occurring in a patient with known colonization by carbapenemase-producing Enterobacterales or Pseudomonas aeruginosa resistant to any antipyocyanic antibiotic or in the event of an outbreak of one of these bacterial infections (panel opinion, strong agreement).

3GCeph R/ESBL-E

Scenario	Carbapenem		BL/BLI		Quin		Aminogl		TMP/SMZ		Fosfo iv		Fosfo oral	
	EU	USA	EU	USA	EU	USA	EU	USA	EU	USA	EU	USA	EU	USA
BSI/cIAI/HAP/VAP Severe or cUTI with septic shock	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	No
BSI/cIAI/HAP/VAP non severe high risk	Yes*	Yes*	No	No	No	No	No	No	No	No	No	No	No	No
BSI/CIAI/HAP/VAP any severity Stabilized step down	No	ND	Yes	ND	Yes	Yes	No	ND	Yes@	Yes	No	ND	No	ND
BSI/c IAI/HAP/VAP non severe low risk	No	Yes	Yes	No»	Yes	Yes£	No	No	Yes	Yes£	No	No	No	No
cUTI w/o Septic shock	No	Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes$	Yes	ND	Yes	Yes
Citrobacter and Enteropbacter with high risk of inducible AmpC	ND	Yes	ND	No	ND	Yes	ND	Yes§	ND	Yes#	ND	No	ND	No

BSI: Blood Stream Infection; cIAI complicated Intra Abdominal infection) HAP Healthcare associated pneumonia VAP Ventilator associated pneumonia) Severe infections: Sepsis or Septic Shock; Low Risk infections All infections originating from UTI (even BSI) or from biliary tract with source control High risk all others. Nd not defined * Ertapenem w/o septic shock @ cUTI with shock § Single dose in UTI $ consider also Nitrofurantoine for cystitis # Cefepime and Nitrofurantoine per UTI £ only as step down therapy “ only as step down therapy for cystitis

CRE

In patients with infections caused by carbapenem-resistant Enterobacterales (CRE), rapid testing should be used to identify specific carbapenemase families (e.g. KPC, NDM, VIM, OXA-48-like). Clinicians should adopt different treatment strategies based on the type of causative carbapenemase-producing Enterobacterales (CPE).


International Journal of Antimicrobial Agents

Scenario	CAZ/AVI			MER/VBR			IMI/RELE			Cefiderocol			Tigecycline			OLD Drugs*			Combo			Carbapenem ext infusion in combo		
	IT	EU	US	IT	EU	US	IT	EU	US	IT	EU	US	IT	EU	US	IT	EU	US	IT	EU	US	IT	EU	US
Severe infections	Yes!	Yes	Yes	Yes!	Yes	Yes !	Yes!	No	Yes!	Yes!	No	Yes§	No	Yes*	Yes*	No	No	No	IE	IEˆ	IE@	No	^	No
Non Severe Infections	Yes	No	Yes	Yes !	No	Yes !	Yes!	No	Yes!	Yes!	No	Yes	No	Yes*	Yes*	No	Yes	No	IE	IEˆ	IE@	No	^	No
MBL	Yes°	Yes°	Yes °	No	No	No	No	No	No	No	Yes	Yes	No	No	No	No	Yes°	Yes °	IE	IEˆ	IE@	No	^	No
cUTI	ND	No	Yes	ND	No	Yes	ND	No	Yes	ND	No	Yes	ND	No	No	ND	Yes	No	IE	IEˆ	IE@	No	^	No

OLD ANTIBIOTICS Aminoglycosides (cUTI single dose in cystitis), Colistin (not for IDSA guidelines) , TMP/SMZ (only IDSA) iv Fosfomycin (only ECDC always in combo) Aztreonam

Severe infections: Sepsis or Septic Shock; MBL Metallo Beta Lactamase cUTI complicated Urinary tract Infection IE Insufficient Evidence for or against

§only in cUTI

*** Only in cIAI ˆCombination therapy if new drugs not available or sensitivity only to polymyxins, aminoglycosides, tigecycline or fosfomycin,**

@ Aminoglycosides suggested in cUTI + in combination with aztreonam

° aztreonam in combination with ceftazidime avibactam

! Not for OXA-48

^ Consider if MIC ≤ 8

J Antimicrob Chemother
https://doi.org/10.1093/jac/dkad206

Meropenem/vaborbactam plus aztreonam for the treatment of New Delhi metallo-β-lactamase-producing *Klebsiella pneumoniae* infections

Giusy Tiseo [1], Lorenzo Roberto Suardi[1], Alessandro Leonildi[2], Cesira Giordano[2], Simona Barnini[2] and Marco Falcone [1]*

[1]*Infectious Diseases Unit, Department of Clinical and Experimental Medicine, Azienda Ospedaliera Universitaria Pisana, University of Pisa, Via Paradisa 2, 56124, Pisa, Italy;* [2]*Microbiology Unit, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy*

*Corresponding author. E-mail: marco.falcone@unipi.t

Difficult To –treat Resistance (DTR)/ Carbapenem Resistant (CR) Pseudomonas aeruginosa (PA)

Scenario	CFTZ/TZB			CAZ/AVI			MER/VBR			IMI/RELE			Cefiderocol			OLD Drugs*			Combo		
	IT	EU	US	IT	EU	US	IT	EU	US	IT	EU	US	IT	EU	US	IT	EU	US	IT	EU	US
Severe infections or high risk	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	No	Yes §	Yes	No	No	IE ^	IE$	IE*
Non Severe Infections and low risk infections	Yes	No	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	No	Yes §	Yes	Yes	No*	IE^	IE@	IE*

Severe infections: Sepsis or Septic Shock;
Low Risk infections All infections originating from UTI (even BSI) or from biliary tract with source control
High risk all others;
§ only UTI ^ Insufficient Evidence for Combo in this settimg $ Aminoglycoside monodose considered in UTI @ Combo if drug chosen is Colistin or Fosfomycin or Aminoglycosides * Combo with Aminoglycosides if drug used MIC close to breakpoint ^ Combo considered on case by case basis exp with Fosfomycin

Carbapenem Resistant Acinetobacter baumanii (CRAB)

Scenario	Ampicillin/ Sulbactam		Cefiderocol		Polimyxins in combo w/o Mer or Rifampins		Tigecycline HD for cIAI w/o BSI		Minocycline		Meropenem Extended infusion in combo if MIC ≤ 8		Aminoglycosydes		Fosfomycin or Rifampicin or aerosolized antibiotics		Combo with at least 2 active agents	
	ECDC	IDSA	ECDC	IDSA	ECDC	IDSA	ECDC	IDSA	ECDC	IDSA	ECDC	IDSA	ECDC	IDSA	ECDC	IDSA	ECDC	IDSA
Sulbactam sensitive non severe low-risk infections	Yes	Yes	No	Yes*	No	Yes*	No	Yes*	NC	Yes*	Yes	No	No	No	No	No	No	No
Sulbactam resistant non severe low risk infections	No	Yes§	No	No	Yes°	No§	Yes	No§	No	No§	Yes	ND	No	No	No	No	No	Yes§
Severe infections	Yes#	Yes$	No	Yes$	Yes#	Yes$	Yes#	Yes$	No	Yes$	Yes#	Yes$	Yes#	Yes$	No	No	Yes#	Yes$

* As alternative to Sulbactam if sensitive in vitro ; § Sulbactam + another active agent ° if sensitive in vitro # At least 2 active agents out of polymyxin, aminoglycoside, tigecycline, sulbactam $ as above + cefiderocol

No convincing data about the optimal antibiotic therapy
Cefiderocol represents a promising antibiotic option but further studies are needed


International Journal of Antimicrobial Agents

Cefiderocol and CRAB : contrasting evidences

STUDY	TYPE OF STUDY	MORTALITY CEFIDEROCOL	MORTALITY COMPARATOR
Bassetti M CREDIBLE-CR, *Lancet Infect Dis, 2021*	RCT	50%	18% (BAT)
Falcone M *Clin Infect Dis 2021*	Observational, case series	10%	NA
Bavaro D *Antibiotics, 2021*	Observational, case series	23%	NA
Pascale R *JAC Antimicrob Res, 2021*	Observational, comparative	55%	58% (COLISTIN)
Falcone M *Antimicrob Agents Chemother 2022*	Observational, comparative	34%	55.8% (COLISTIN)

Synergistic Effect of Cefiderocol Combined With Other Antibiotics

AVIBACTAM (FIC index of 0.026–0.033)

SULBACTAM (FIC index 0.26–0.27)

MEROPENEM sinergistic in 42.9% of CRAB (including PER-producing)

ID Week 2019; Yamano, Session 068, Poster 723
ID Week 2019; Yamano, Poster 1629

Cefiderocol and CRAB

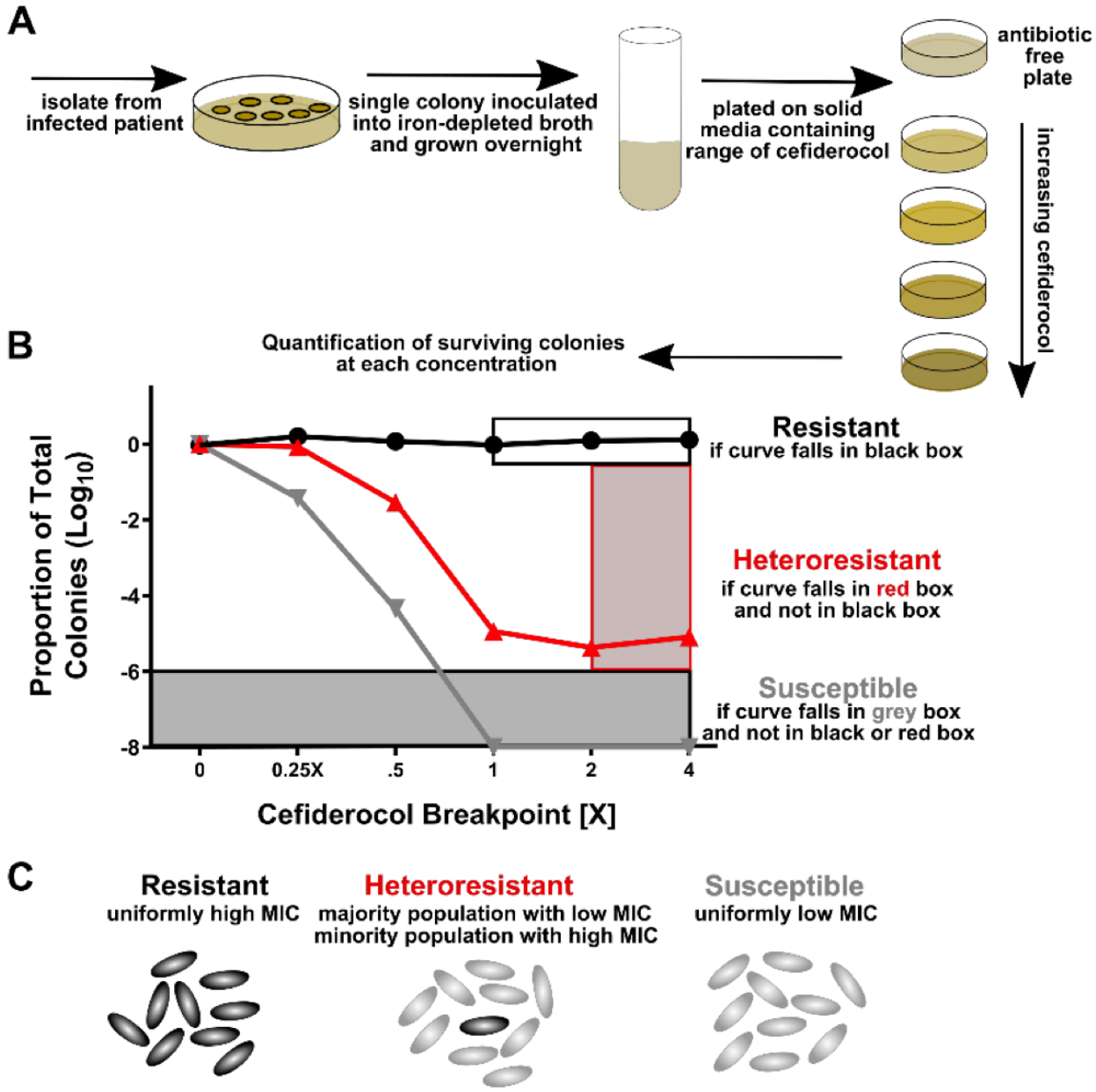
MONOTHERAPY versus COMBINATION

PARTNER ANTIBIOTIC

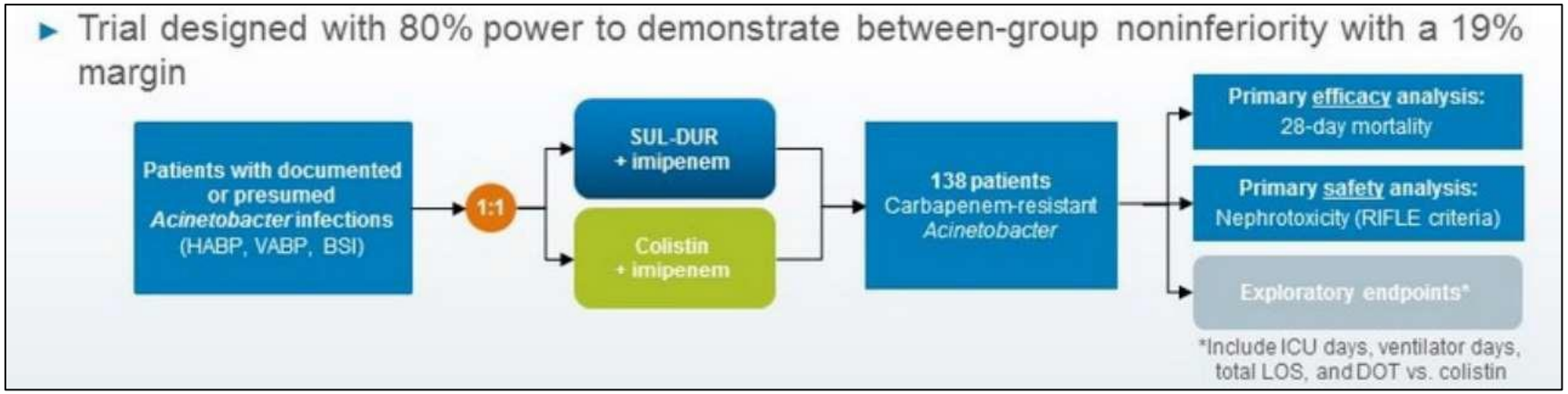
LUNG PENETRATION

ROLE OF HETERORESISTANCE

OCCURRENCE OF RESISTANCE



Durlobactam/sulbactam: ATTACK Phase III Trial



	SUL/DUR	COLISTIN	
28-day mortality	**19%**	**32.3%**	**95% CI (-30.0, 3.5)**
Clinical cure at TOC	**61.9%**	**40.3%**	**95% CI (2.9, 40.3)**
Nephrotoxicity	**13.2%**	**37.6%**	**p<0.001**

Kaye KS, Lancet Infect Dis. 2023:S1473-3099(23)00184-6

Stenotrophomonas maltophila

- Mild infections,
  - TMP-SMX, minocycline preferred
  - Tigecycline, levofloxacin, or cefiderocol alternatives;
  - Ceftazidime is not suggested for the treatment of S. maltophilia regardless of the severity of infection given the intrinsic β-lactamases produced by S. maltophilia likely to render ceftazidime ineffective.
- Moderate to severe infections, any of three
  1. the use of **combination therapy**, with TMP-SMX and minocycline as the preferred combination,
  2. the initiation of **TMP-SMX monotherapy with the addition of a second agent** (minocycline [preferred], tigecycline, levofloxacin, or cefiderocol) if there is a delay in clinical improvement with TMP-SMX alone, or
  3. the **combination of ceftazidime-avibactam and aztreonam**, when intolerance or inactivity of other agents are anticipated.

ummary of recommendations for infections caused by carbapenem-resistant Gram-negative bacteria.[a]

Carbapenem-resistant bacteria	Recommended therapy	Alternative therapy
KPC-producing *Enterobacterales*	Ceftazidime–avibactam (B-II) Meropenem–vaborbactam (B-II)	Imipenem–relebactam (C-III)
OXA-48-producing *Enterobacterales*	Ceftazidime–avibactam (B-II)	Cefiderocol (C-III)
MBL-producing *Enterobacterales*	Ceftazidime–avibactam + aztreonam (B-II)	Cefiderocol (C-III)
Carbapenemase-producing *Enterobacterales* with resistance to new antimicrobials (or if other active drugs are not appropriate for the source of infection, high risk of toxicity or allergy)	Meropenem[b] (B-II) Colistin[c] (B-II) Tigecycline[d] (B-II) Aminoglycosides[e] (B-II)	Double carbapenem[f] (B-III) Fosfomycin[g] (C-III) Cotrimoxazole[h] (C-III)
DTR–*Pseudomonas aeruginosa*[i]	Ceftolozane–tazobactam (B-II)	Ceftazidime–avibactam (C-III) Imipenem–relebactam (C-III) Colistin[j] (B-II), Cefiderocol[k] (B-II) Fosfomycin[l] (C-III)
Carbapenem-resistant *Acinetobacter baumannii*	Sulbactam[m] (C-III)	Colistin[n] (C-III) Minocycline[n] (C-III), Tigecycline[n] (C-III) Aminoglycosides[n] (C-III), Cefiderocol[n] (C-III)
Stenotrophomonas maltophilia	Cotrimoxazole (B-II)	Levofloxacin[o] (B-II)

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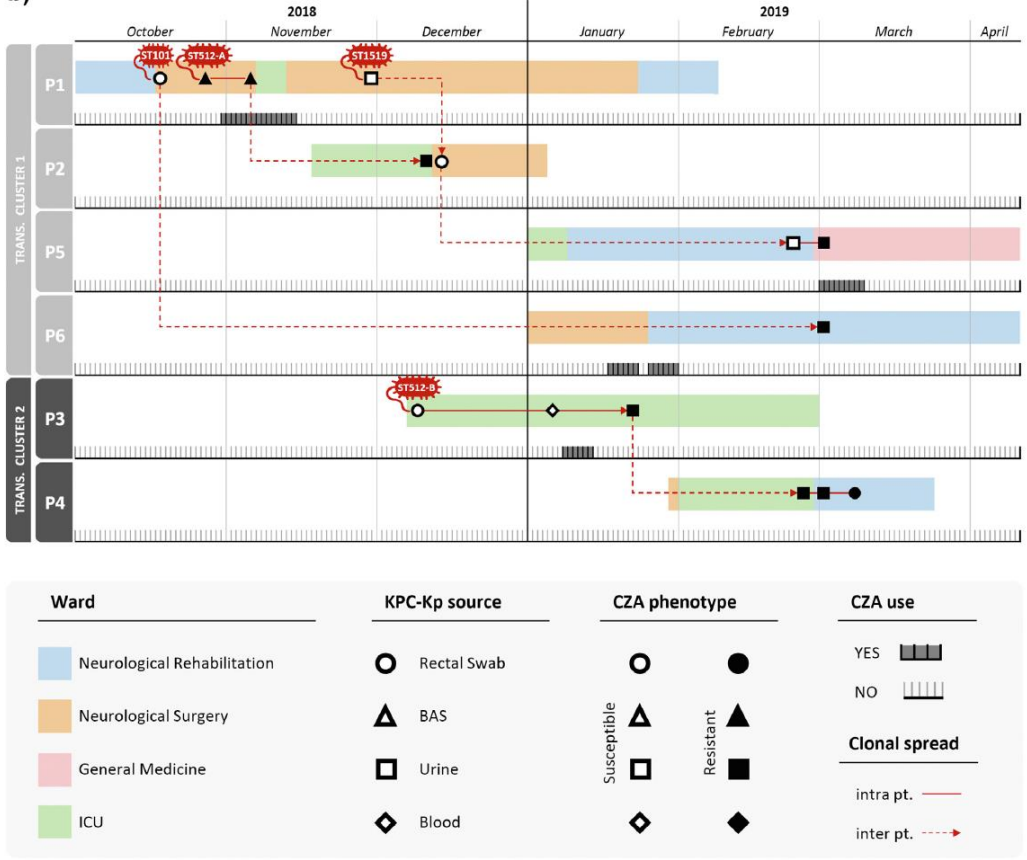
Original article

Deciphering variable resistance to novel carbapenem-based β-lactamase inhibitor combinations in a multi-clonal outbreak caused by *Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae* resistant to ceftazidime/avibactam

Vincenzo Di Pilato [1], Luigi Principe [2, 3], Lilia Andriani [4], Noemi Aiezza [5], Marco Coppi [5, 6], Silvia Ricci [4], Tommaso Giani [5, 6], Francesco Luzzaro [2, 3], Gian Maria Rossolini [5, 6, *]

[1] *Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy*
[2] *Clinical Pathology and Microbiology Unit, "S. Giovanni di Dio" Hospital, Crotone, Italy*
[3] *Clinical Microbiology and Virology Unit, "A. Manzoni" Hospital, Lecco, Italy*
[4] *Clinical Pathology and Microbiology Unit, "Moriggia Pelascini" General Hospital, Gravedona, Italy*
[5] *Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy*
[6] *Clinical Microbiology and Virology Unit, Florence Careggi University Hospital, Florence, Italy*



In this multi-clonal outbreak of KPC-Kp, the overproduction of KPC-3 was the leading mechanism of cross-resistance to CZA and MVB, whereas resistance to IMR appeared less affected. The emergence and dissemination of similar resistance mechanisms may have relevant clinical and diagnostic implications, and their surveillance is warranted.

Open Forum Infectious Diseases

MAJOR ARTICLE

Clinical Characteristics and Outcome of Ceftazidime/Avibactam-Resistant *Klebsiella pneumoniae* Carbapenemase–Producing *Klebsiella pneumoniae* Infections: A Retrospective, Observational, 2-Center Clinical Study

Alessandra Oliva,[1] Laura Campogiani,[2,3] Giulia Savelloni,[1] Pietro Vitale,[2] Alessandra Lodi,[2] Frederica Sacco,[1] Alessandra Imeneo,[3] Lorenzo Volpicelli,[1] Riccardo Polani,[4] Giammarco Raponi,[1] Loredana Sarmati,[2,3] and Mario Venditti[1]

[1]Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy, [2]Infectious Disease Clinic, Policlinico Tor Vergata, Rome, Italy, [3]Department of System Medicine, Tor Vergata University, Rome, Italy, and [4]Department of Molecular Medicine, Sapienza University of Rome, Rome, Italy

Consensus MI Niguarda

Terapia empirica in pz colonizzati o con storia di colonizzazione recente:
- con shock settico o sepsi (sepsis-3)
- con immunodepressione ed infezione sistemica

Terapia mirata in infezioni gravi da G- MDR

- CRAB:
  1. ampicillina/sulbactam + colistina (o fosfomicina)
  2. cefiderocol +/- ampicillina/sulbactam

- P. aeruginosa DTR
  - ceftolozano/tazobactam +/- aminoglicoside/fosfomicina

- KPC
  - Severe cUTI o BSI > ceftazidime/avibactam
  - HAP > meropenem/vaborbactam
  - cIAI
    - colangiti: ceftazidime/avibactam + tigeciclina
    - raccolte addominali: meropenem/vaborbactam + tigeciclina/linezolid
- MBL
  - VIM > cefiderocol o ceftazidime/avibacatm + aztreonam
  - NDM > ceftazidime/avibactam + aztreonam

Nelle infezioni non gravi quando possibile vengono impiegati “old antibiotics”
i.e. e Aminoglicosidi o Fosfomicina monoterapia in cUTI

Place in therapy of new antibiotics from new molecules to long acting strategies

- New drugs for MDR G-
  - Ceftazidime/avibactam
  - Ceftolozano/tazobactam
  - Cefiderocol
  - Meropenem/vaborbactam
  - Imipenem/relebactam

- Long acting strategies for G+
  - Dalbavancin
  - Oritavancin

What is the recommended treatment for methicillin-resistant Staphylococcus aureus (MRSA) infections?

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Review

Diagnosis and management of infections caused by multidrug-resistant bacteria: guideline endorsed by the Italian Society of Infection and Tropical Diseases (SIMIT), the Italian Society of Anti-Infective Therapy (SITA), the Italian Group for Antimicrobial Stewardship (GISA), the Italian Association of Clinical Microbiologists (AMCLI) and the Italian Society of Microbiology (SIM)

Giusy Tiseo[a,1], Gioconda Brigante[b,1], Daniele Roberto Giacobbe[c,d,1], Alberto Enrico Maraolo[e,1], Floriana Gona[f,1], Marco Falcone[g], Maddalena Giannella[h,i], Paolo Grossi[j], Federico Pea[k,l], Gian Maria Rossolini[m], Maurizio Sanguinetti[n], Mario Sarti[m], Claudio Scarparo[o], Mario Tumbarello[p], Mario Venditti[q], Pierluigi Viale[a,b], Matteo Bassetti[c,d,r], Francesco Luzzaro[s,t], Francesco Menichetti[u,v,*], Stefania Stefani[f,r], Marco Tinelli[s,t]

Antibiotic	SSTI	CAP	HCAP	VAP	BSI
Vancomycin					
Daptomycin					
Dalbavancin					
Oritavancin					
Delafloxacine					
Ceftobiprole					
Ceftaroline					
Linezolid					
Tedizolid					
TMP/SMZ	Mild uncomplicated	**Monotherapy should not be used for severe infections**			
Clindamycin					
Combo + Fosfomycin					
Combo + Ceftaroline /Ceftobiprole or Betalactam					

Main PK/PD characteristics against MRSA

Antimicrobial	Protein binding (%)	Volume of distribution	Terminal half-life (h)	Main PD parameter correlating with efficacy	Suggested AUC/MIC value against MRSA
Vancomycin	50 – 55	0.4 – 1 l/kg	6 – 12	AUC/MIC	> 400-severe infections > 200-cSSTIs
Teicoplanin	90	0.7 – 1.4 l/kg	100 – 170	AUC/MIC	> 900
Dalbavancin	93		240	AUC/MIC	> 100 – 300
Oritavancin	85		245	AUC/MIC	> 90 – 110

Grupper M & Nicolau DP, Curr Opin Infect Dis, 2017

General features of dalba vs orita

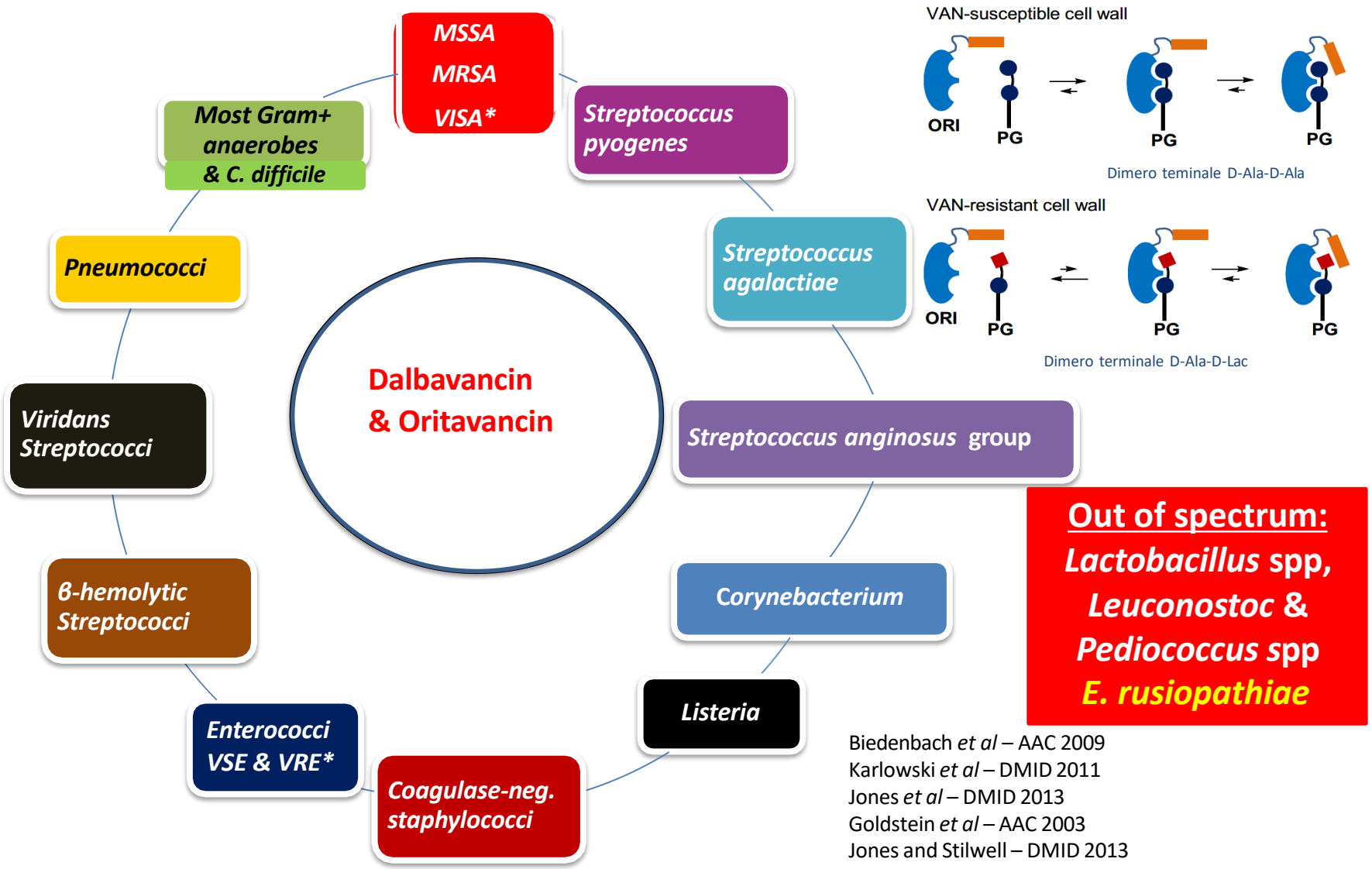
Characteristics	Dalbavancin	Oritavancin
FDA indication	ABSSSI	ABSSSI
Dosing FDA approved	1.5g single 1g followed by 0.5 at day 8	1.2g single
Infusion time	0.5 hours	3 hours
Renal dose adjustment	CrCl<30ml/min	CrCl<30ml/min
Drug-drug interaction	no clinically relevant	no clinically relevant
Other		Interference with blood coagulation test

In vitro activity of glico/lipopeptides

	MIC_{90} (µg/mL)			
Pathogen (n)	**Oritavancin**	**Vancomycin**	**Daptomycin**	**Dalbavancin**
S. aureus (13,336)	0.06	1	0.5	0.06
MSSA (7,800)	0.06	1	0.5	0.06
MRSA (5,536)	0.06	1	0.5	0.06
β streptococci (2,281)	0.12	0.5	0.25	0.03
E. faecalis (2,132)	0.06	2	1	0.06
E. faecium (1,237)	0.06	>16	2	0.12
S. pneumoniae	<=0.01	0.25	0.25	0.008
C. striatum & jeikeium	0.06	0.25	**KO!**	0.12
E. rhusiopathiae	4	>256	16	**?**

literature review from: Crotty MP et al *J Clin Microbiol* 2016, Biavasco F & Varaldo P et al *AAC*, 1997; Mendes et al *JAC*, 2014; Venditti M et al *AAC*, 1990

Dalbavancin & Oritavancin – The overall spectrum

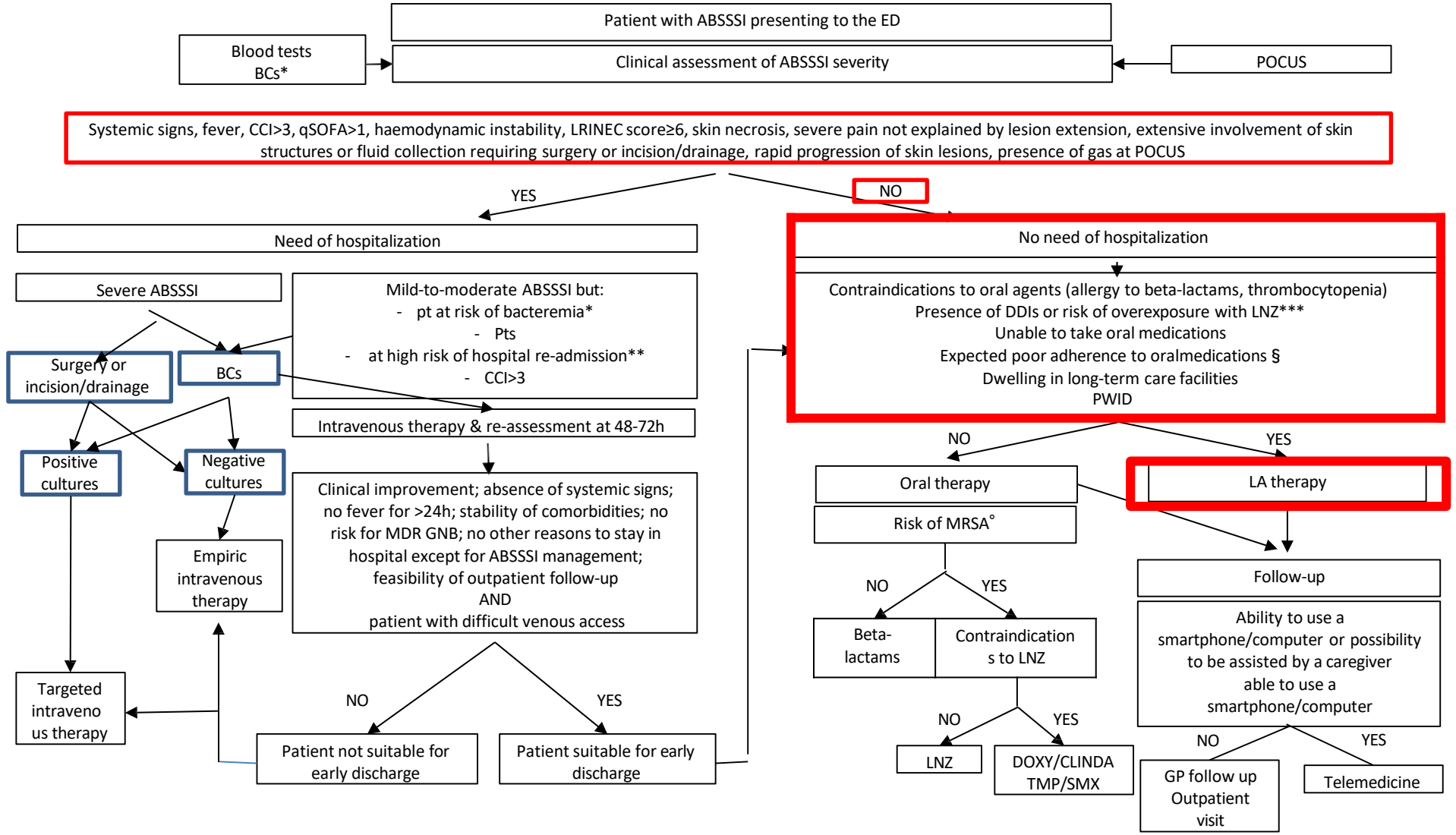


<u>Out of spectrum:</u>
***Lactobacillus* spp,**
***Leuconostoc* &**
***Pediococcus* spp**
E. rusiopathiae

Biedenbach *et al* – AAC 2009
Karlowski *et al* – DMID 2011
Jones *et al* – DMID 2013
Goldstein *et al* – AAC 2003
Jones and Stilwell – DMID 2013

* Dalbavancin active only vs Van-B producers VRE & VISA

Direct or early discharge of ABSSSI patients from the Emergency Department/Unit: place on therapy of Dalbavancin



Oliva et al *Exp Rev Antifect ther,* 2023

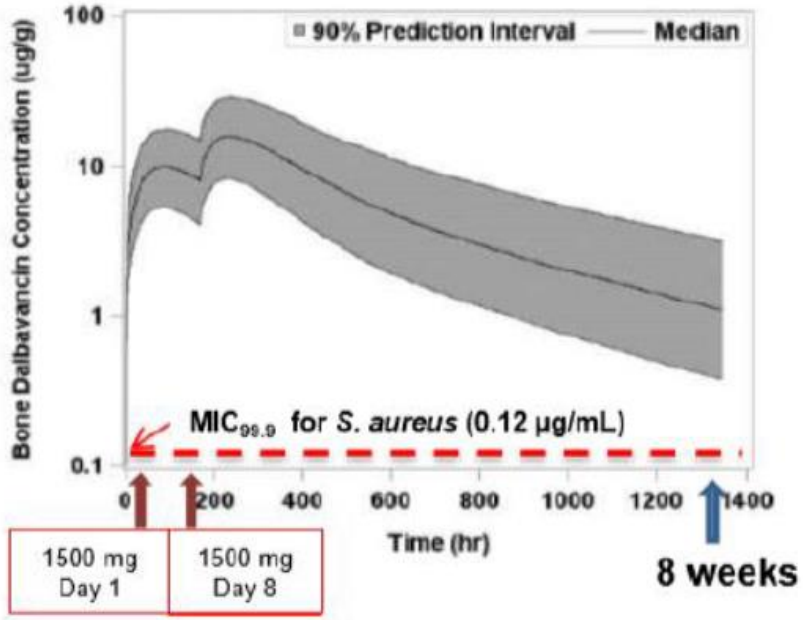
Newer glycopeptide antibiotics for treatment of cSSTIs : a systematic review, network meta- analysis and cost analysis

- **Seven RCTs met inclusion criteria in the network meta-analyses.**
- **Data suggested that the clinical response to dalbavancin or oritavancin was similar to standard care (OR 0.78, CI 0.52-1.18; and OR 1.06, CI 0.85-1.33)**
- **Head-to-head comparisons showed no difference in clinical response between oritavancin and dalbavancin (OR 1.36; CI 0.85-2.18). Studies were of high quality overall.**
- **Our cost analyses demonstrated that dalbavancin and oritavancin were less costly compared to standard care under baseline assumptions and many scenarios evaluated.**
- **The use of dalbavancin could save third-party payers $1,442 to $4,803 per cSSTI, while the use of oritavancin could save $3,571 to $6,932 per cSSTI.**

Agarwal et al *Clin Microbiol Infect*, 2018

Costo terapia anti-Gram+

Linezolid	**600 mg x 2 OS**	**1.94**
Vancomicina	**500 mg x 4 EV**	**3.62**
Linezolid	**600 mg x 2 EV**	**8.16**
Co-trimossazolo	**2 fl x 3**	**11.55**
Oxacillina	**3 g x 4**	**17.95**
Teicoplanina	**800 mg**	**32.96**
Ceftarolina	**600 mg x 2**	**103.04**
Tigeciclina	**50 mg x 2**	**104.56**
Daptomicina	**500 mg**	**107.20**
Tedizolid	**200 mg**	**120.02**
Ceftobiprolo	**500 mg x 3**	**159.63**
Dalbavancina	**1500 mg**	**1276.24**



45.50 € / die

Average antibiotics concentrations into bone and joint tissues

Agent	cancellous bone	cortical bone	joint
Clindamycin	6.9 ug/mL	6.9 ug/mL	2 ug/mL
Linezolid	6.4 ug/mL	6.4 ug/mL	4 ug/mL
Vancomycin	3.8 ug/mL	4.5 ug/mL	……
Daptomycin	21.4 ug/mL	21.4 ug/mL	21.6 ug/mL
Dalbavancin	13.4 ug/mL.	4.2 ug/mL	……
Oritavancin	27.0 ug/mL	65.6 ug/mL	……

Thabit et al International Journal of Infectious Diseases 81 (2019) 128–136

In vitro activity of oritavancin in combo with rifa or genta against prosthetic 20 joint infection-associated MRSE biofilms

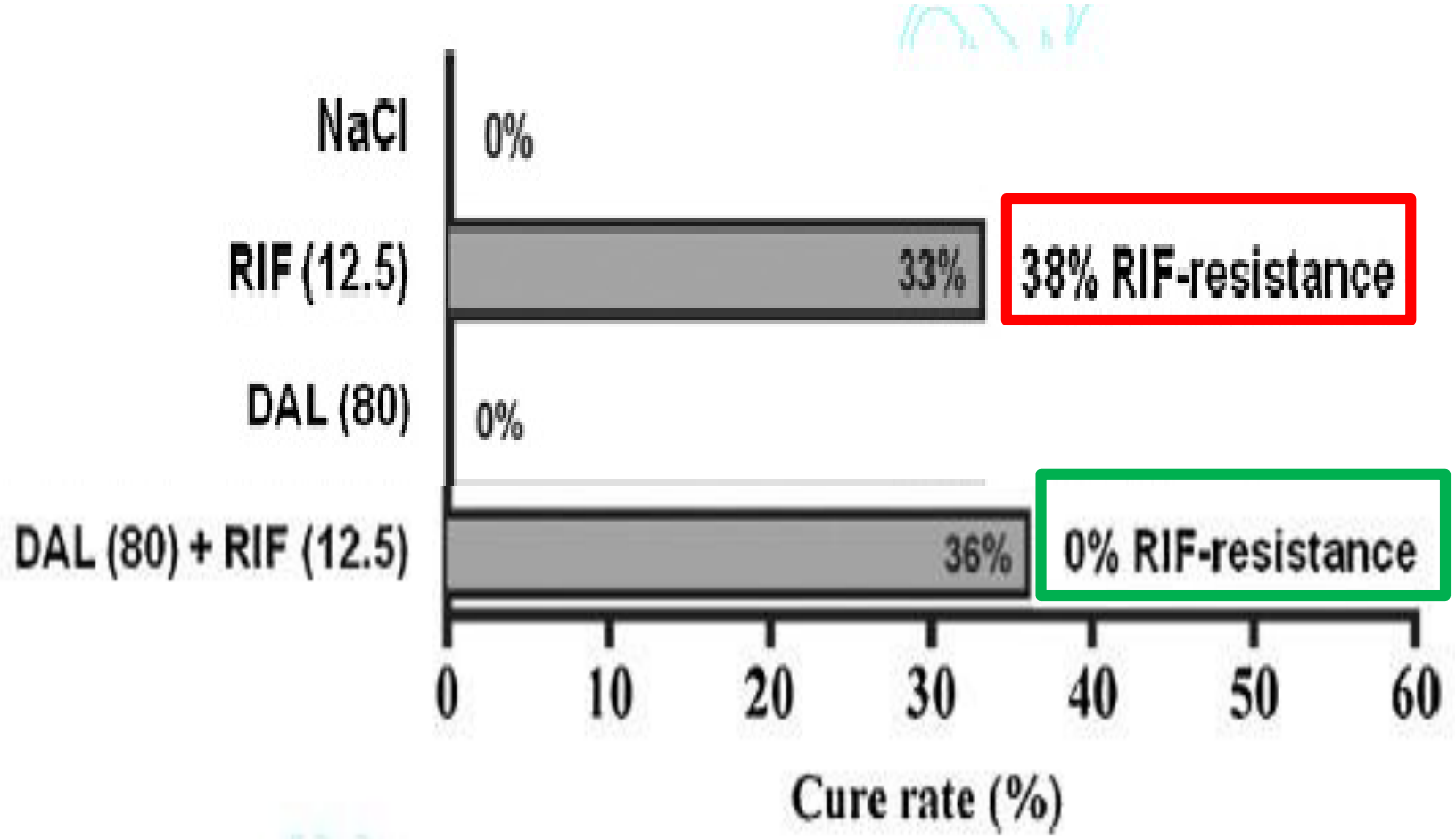
Time kill studies

Agents alone/combo	% bactericidal activity at 24 h	
	overall	No cultures detection
Oritavancin	5%	0%
Rifampicin	25%	0%
Oritavancin+Rifampicin	85%	50%

Yan Q et al *IJAA*, 2018

Activity of dalba, alone and in combo with rifa, against MRSA in a foreign-body infection model

Cure rate of cage associated infections at day 12



Baldoni D et al *Intern J Antimicrob Agents*, 2013

Treatment of osteoarticular, cardiovascular, intravascular- catheter-related and other complicated infections with dalbavancin and oritavancin: A systematic review

- **The single most common off-label indication for oritavancin and dalbavancin in 38 studies was osteoarticular infection, with a median success rate of 73% [IQR 58–85%] among the 14 studies with more than one patient…..**
- **….followed by IE: the overall success rate for NVE/PVE & PM infections was 68% (IQR 56–86%) among 9 studies.**
- **the success rate for catheter-related BSI was 75% (IQR 59–90%) among seven studies.**

Geren et al IJAA, 2021

Cumulative Efficacy Reported with the Use of Dalbavancin for off-Label Therapeutic Indications

Off-Label Therapeutic Indications	Clinical Success	Relapse	Resistance Development
Endocarditis	120/148 (81.1%)	7/114(6.1%)	3/114(2.6%)
Bloodstream infections	117/144(81.3%)	7/140(5.0%)	1/140(0.7%)
Bone and joint infections	408/483(84.5%)	31/387(8.0%)	0/387(0.0%)
Others	23/25(92.0%)	2/25(8.0%)	0/25(0.0%)
Deep sternal wound infections	15/16(93.8%)	1/16(6.2%)	0/16(0.0%)
Intrabdominal infection	3/3(100.0%)	0/3(0.0%)	0/3(0.0%)
Mediastinitis	1/2(50.0%)	1/2(50.0%)	0/2(0.0%)
Pneumonia	2/2(100.0%)	0/2(0.0%)	0/2(0.0%)
Sinusitis	1/1(100.0%)	0/1(0.0%)	0/1(0.0%)
Pyelonephritis	1/1(100.0%)	0/1(0.0%)	0/1(0.0%)

Gatti M et al *Drug Design, Development and Therapy* 2021:15 3349–3378

ESC European Society of Cardiology
European Heart Journal (2023) 00, 1–95
https://doi.org/10.1093/eurheartj/ehad193
ESC GUIDELINES

2023 ESC Guidelines for the management of endocarditis

Developed by the task force on the management of endocarditis of the European Society of Cardiology (ESC)

Endorsed by the European Association for Cardio-Thoracic Surgery (EACTS) and the European Association of Nuclear Medicine (EANM)

Authors/Task Force Members: Victoria Delgado *†, (Chairperson) (Spain), Nina Ajmone Marsan ‡, (Task Force Co-ordinator) (Netherlands), Suzanne de Waha‡, (Task Force Co-ordinator) (Germany), Nikolaos Bonaros (Austria), Margarita Brida (Croatia), Haran Burri (Switzerland), Stefano Caselli (Switzerland), Torsten Doenst (Germany), Stephane Ederhy (France), Paola Anna Erba [1] (Italy), Dan Foldager (Denmark), Emil L. Fosbøl (Denmark), Jan Kovac (United Kingdom), Carlos A. Mestres (South Africa), Owen I. Miller (United Kingdom), Jose M. Miro [2] (Spain), Michal Pazdernik (Czech Republic), Maria Nazarena Pizzi (Spain), Eduard Quintana [3] (Spain), Trine Bernholdt Rasmussen (Denmark), Arsen D. Ristić (Serbia), Josep Rodés-Cabau (Canada), Alessandro Sionis (Spain), Liesl Joanna Zühlke (South Africa), Michael A. Borger *†, (Chairperson) (Germany), and ESC Scientific Document Group

(viii) Data on the efficacy of long-term antibiotic suppressive therapy in patients with IE who do not undergo cardiac surgery are limited to small and heterogeneous series with various antibiotic regimens.[184,274] In a small series of Gram-positive bloodstream infections and IE, dalbavancin (500 mg weekly or 1000 mg biweekly regimens) has been shown effective.[274,275] Relapses are not infrequent.[184]

7.13.2. Other considerations for outpatient oral or parenteral antimicrobial therapy

or in continuous infusion. Dalbavancin is a glycopeptide antibiotic with a very long half-life that can be administered weekly. There is previous positive experience in sensitive Gram-positive IE, although the most effective administration schedule is not clear.[274,402] The recommended prescription is 1.5 g as a loading dose followed by 0.5–1 g weekly until completing 6 weeks of antibiotic treatment.

Antibiotic concentrations in ELF and alveolar macrophage cells comparing to serum levels

Antibiotic	Dose	Time (hr)	ELF (mg/L)	Cells (mg/L)	C_{ELF}/C_{fs} [b] or AUC_{ELF}/AUC_{fs} [c]	C_{cell}/C_{fs} [d] or AUC_{cell}/AUC_{fs} [e]	Comments
Oritavancin	800 mg q24 IV, 5 days	AUC_{24}	106	3 297	4.6	142.7	Healthy Volunteers
Linezolid	600 mg q12 PO, 5doses	AUC_{24}	622.8	27.2	4.77	0.22	Healthy Volunteers
Vancomycin	1g q12 IV, 9 doses	AUC_{24}	92	926	0.56	5.6	Healthy Volunteers

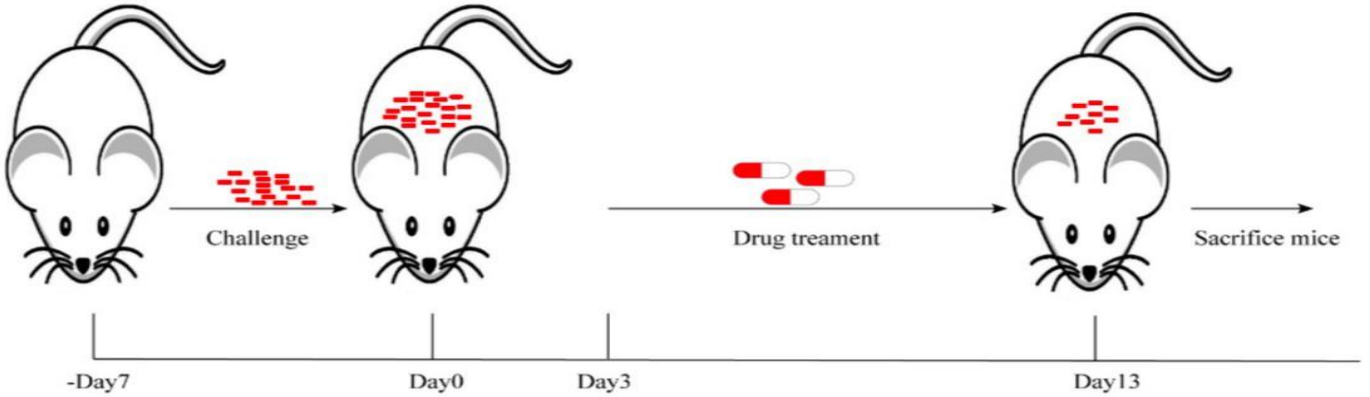
Kiem & Schentag Infect Chemother, 2014

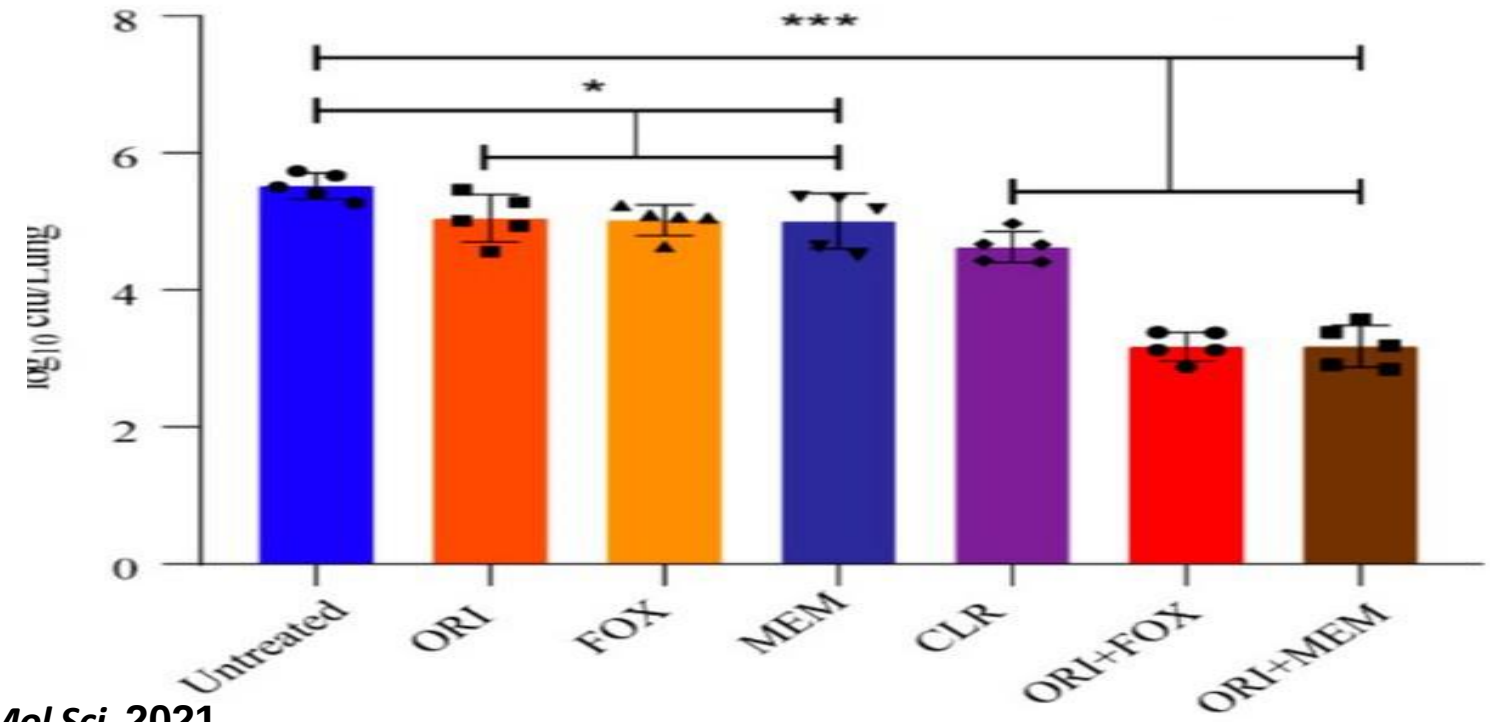
Activity of Oritavancin and Its Synergy with Other Antibiotics against *Mycobacterium abscessus* Infection In Vitro and In Vivo

- **In vitro studies: Oritavancin exhibited time-concentration dependent bactericidal activity not only against *M. abscessus* (MIC 8mg/l) but also against reference strains of *M. bovis* BCG (MIC 0.125-0.5) and *M tuberculosis* (MIC 0.125-2 mg/l) and also displayed synergy with clarithromycin, tigecycline, cefoxitin, moxifloxacin, and meropenem.**
- **Intracelluar activity studies: Oritavancin had bactericidal effect on intracellular *M. abscessus*.**
- **Animal studies: Oritavancin significantly reduced bacterial load in lung when it was used alone or in combination with cefoxitin and meropenem.**
- **Conclusions: oritavancin may be a viable treatment option against *M. abscessus* infection.**

Wang et al Int J Mol Sci. 2021

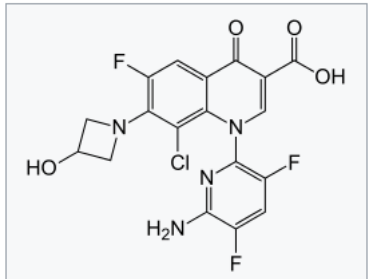
Activity of Oritavancin and Its Synergy with Other Antibiotics against *Mycobacterium abscessus* Infection In Vitro and In Vivo





Wang et *al* *Int J Mol Sci.* 2021

Delafloxacin



Clinical data	
Trade names	Baxdela, Quofenix
Other names	ABT-492; RX-3341; WQ-3034
AHFS/Drugs.com	Monograph
License data	EU EMA: by INN US DailyMed: Delafloxacin
Routes of administration	By mouth, intravenous injection
ATC code	J01MA23 (WHO)

Active on MRSA in ABSSTI but not in CAP

Infection and Drug Resistance

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ORIGINAL RESEARCH

Efficacy and safety of delafloxacin in the treatment of acute bacterial skin and skin structure infections: a systematic review and meta-analysis of randomized controlled trials

This article was published in the following Dove Press journal:
Infection and Drug Resistance

Table 1 Characteristics of included studies

Study, year published	Study design	Study site	Study period	Study population	Number of patients		Dose regimen	
					Delafloxacin	Comparator	Delafloxacin	Comparator
O'Riordan et al, 2015[13]	Multicenter, randomized, double-blind trial	14 sites in USA	Between June and September 2008	Complicated skin and skin structure infection	49 (300 mg) 51 (450 mg)	50	Delafloxacin, 300 mg or 450 mg q12 h	Tigecycline 100 mg IV x 1, followed by 50 mg IV q12 h
Kingsley et al, 2016[11]	Multicenter, randomized, double-blind trial	23 center in USA	Between February and November, 2011	Acute bacterial skin and skin structureinfection (ABSSSI)	81 (300 mg)	77 (Linezolid) 98 (Vancomycin)	Delafloxacin 300 mg q12 h	Linezolid 600 mg or vancomycin 15 mg/kg
Pullman et al, 2017[14]	Multicenter, randomized, double-blind trial	34 center in seven countries	Between April 2013 and June, 2014	ABSSSI	331 (300 mg)	329	Delafloxacin 300 mg q12 h	Vancomycin 15 mg/kg plus aztreonam 2 g q12 h
O'Riordan et al, 2018[12]	Multicenter, randomized, double-blind trial	76 center in 16 countries	Between May 2014 and January, 2016	ABSSSI	423 (300 mg)	427	Delafloxacin 300 mg q12 h	Vancomycin 15 mg/kg plus aztreonam 2 g q12 h

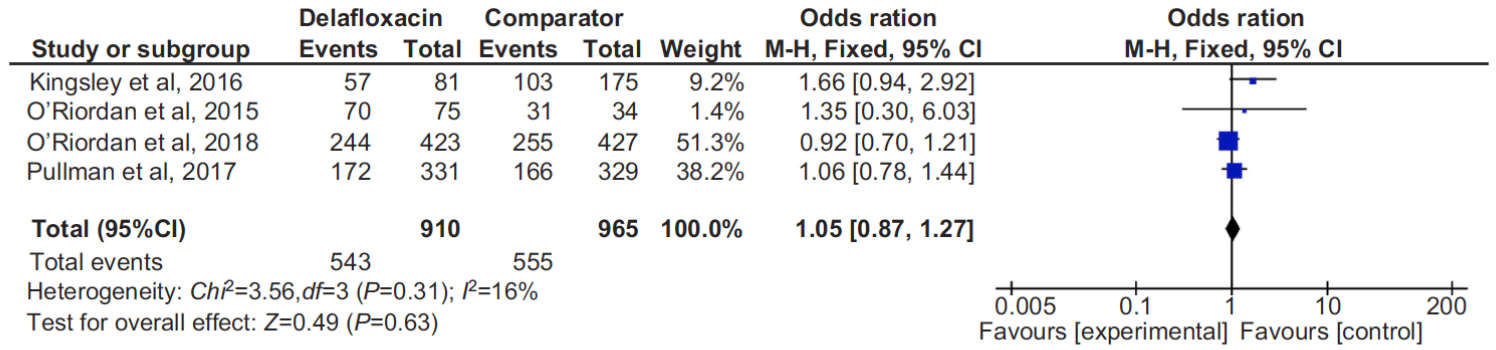

Figure 4 Overall clinical cure rates of delafloxacin and comparators in the treatment of acute bacterial skin and skin structure infections.

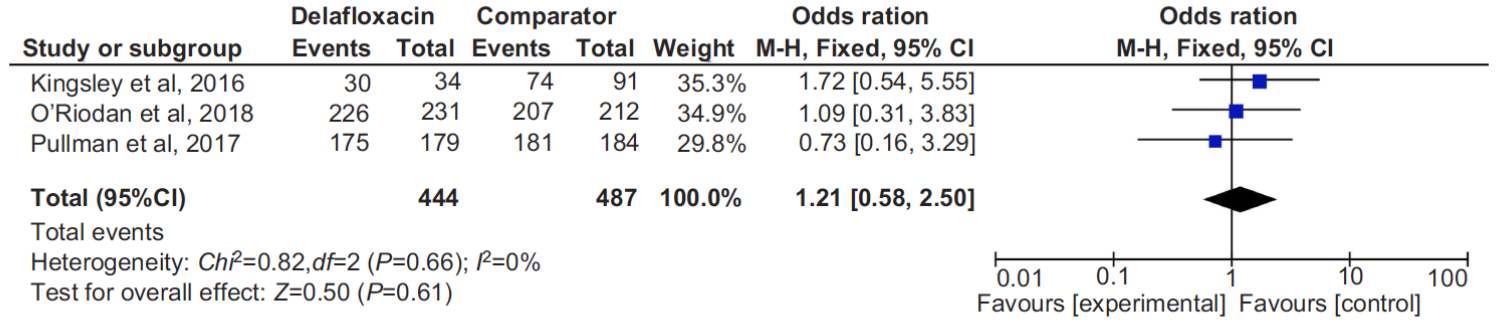

Figure 5 Overall microbiological eradication rates of delafloxacin and comparators in the treatment of acute bacterial skin and skin structure infections.

Question 1. Do rapid microbiological diagnostics impact on the management and clinical outcome of critically ill/septic patients?

Recommendations	Strength	Certainty
In critically ill patients, the use of rapid diagnostic microbiological tests (RDTs) should be adopted since they have the potential to improve the timing to initiate appropriate therapy and possibly improve the patient outcome.	STRONG	LOW
In patients colonised or potentially infected with extended- spectrum β-lactamase (ESBL)-producing and/or carbapenem-resistant Enterobacterales (CRE), the use of molecular tests should be adopted since it is associated with a more rapid administration of appropriate antimicrobial therapy and can lead to a reduction in mortality.	STRONG	LOW
Rapid molecular identification of micro-organisms from blood cultures as well as rapid detection of their resistance mechanisms should be carefully integrated in the laboratory workflow scheme. These tests may be useful tools for 24 hour/day monitored care.	STRONG	MOD

Question 2: Do rapid microbiological diagnostics favour the adjustment of empirical therapy and the transition to targeted therapy?

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Review

Diagnosis and management of infections caused by multidrug-resistant bacteria: guideline endorsed by the Italian Society of Infection and Tropical Diseases (SIMIT), the Italian Society of Anti-Infective Therapy (SITA), the Italian Group for Antimicrobial Stewardship (GISA), the Italian Association of Clinical Microbiologists (AMCLI) and the Italian Society of Microbiology (SIM)

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Recommendations	Strength	Certainty
In hospitalised patients, the use of rapid diagnostic tests (RDTs) is recommended to improve time to initiate appropriate antimicro- bial therapy.	STRONG	LOW
Rapid diagnostic tests (RDTs) are recommended for improving time to effective therapy in bloodstream infections (BSIs) caused by resistant organisms, particularly vancomycin-resistant en- terococci (VRE), methicillin-resistant Staphylococcus aureus (MRSA), multidrug-resistant Pseudomonas aeruginosa, and extended-spectrum β-lactamase (ESBL)- and carbapenemase-producing Enterobacterales.	STRONG	LOW
The implementation of rapid diagnostic tests (RDTs) **should include activation of an antimicrobial stewardship programme (ASP)** (including an action plan to ensure correct interpretation, real-time reporting and guidance on optimal therapy).	STRONG	MOD
The use of rapid diagnostic tests (RDTs) is recommended since it can lead to a more judicious use of antibiotics; it should be **part of the standard of care in patients with bloodstream infections (BSIs)**.	COND	LOW

Question 3: Does rapid microbial identification reduce the duration of therapy and the length of stay (LOS) in infections caused by multidrug-resistant bacteria?

Recommendations	Strength	Certainty
In hospitalised patients, the use of rapid diagnostic methods is suggested to decrease hospital length of stay (LOS), improving the outcome of patients requiring a change in therapy.	STRONG	LOW
Implementing molecular rapid diagnostic testing (mRDT) with an antimicrobial stewardship programme (ASP) can reduce time to effective therapy and length of stay (LOS) in patients with bloodstream infections (BSIs) caused by multidrug-resistant bacteria. Effectiveness was demonstrated in a 24-h/7-day laboratory organisation.	COND	LOW

Question 4: Does knowledge of local/regional/national epidemiology favour the implementation of rational empirical therapy?

Recommendations	Strength	Certainty
Updated local antibiograms with pathogen-specific susceptibility data should be produced at least annually together with data on antimicrobial use to optimise expert-based recommendations for empirical therapy. First evidence of the importance of the preliminary report.	STRONG	MOD

Question 9: What is the role of therapeutic drug monitoring (TDM) in the antimicrobial therapy of multidrug-resistant organism (MDRO) infections?

Drug	Recommendation	Strength	Certainty
Vancomycin	Should be used	STRONG	LOW
β-lactams,	Plays an important role (decrease resistance)	GOOD PRACTICE STATEMENT	
Linezolid	Should be routinely performed when used in critically ill patients		
Teicoplanin			
Daptomycin			
Aminoglycosides			

Question 10. What is the role of **follow-up blood cultures (FUBCs)** in the management of multidrug-resistant organ- ism bloodstream infection (MDRO-BSI)?

Bacteria	FUBC in BSI	Strength	Certainty
MRSA	may positively impact on relevant clinical outcomes	STRONG	LOW
VRE	may positively influence important clinical outcomes	COND.	VERY LOW
GRAM -	may have a useful prognostic role, especially in case of severe and/or high-inoculum infections, non-eradicable foci or immunosuppressed patients.		

Place in therapy of new antibiotics, from new molecules to long acting strategies
Key messages

- Role of new anti MDR G- antibiotics in empiric therapy is still controversial
- Targeted therapy EU guidelines → sparing strategy for new antibiotics active on anti G- MDR <> US and Italian guidelines
- Dalbavancin and Oritavancin are more than only long acting drug: wide spectrum of action, potency, biofilm and foreign bodies in synergy with RFP, good penetration in bone and joints, global cost-effectiveness
- Dalbavancin and oritavancin 1st line or discharge therapy in a minority of SSTI
- Off label use in endocarditis and bone/joints infection is a real world practice
- In order to optimize these new tools:
  - Implementation of RDT in lab
  - TDM
  - Follow up culture

NOVEL DATA ON NEW AND OLD EPIDEMICS

CONFERENCE

Milan, 12 September 2023

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