AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

Nuovi Antibiotici per il Trattamento delle Infezioni da Gram-positivi

SITA Firenze 3 Dicembre 2021

Francesco G. De Rosa
City of Health and Science
University of Turin, Italy
Cardinal Massaia Hospital, Asti
Fellow, Infectious DIseases Society of America

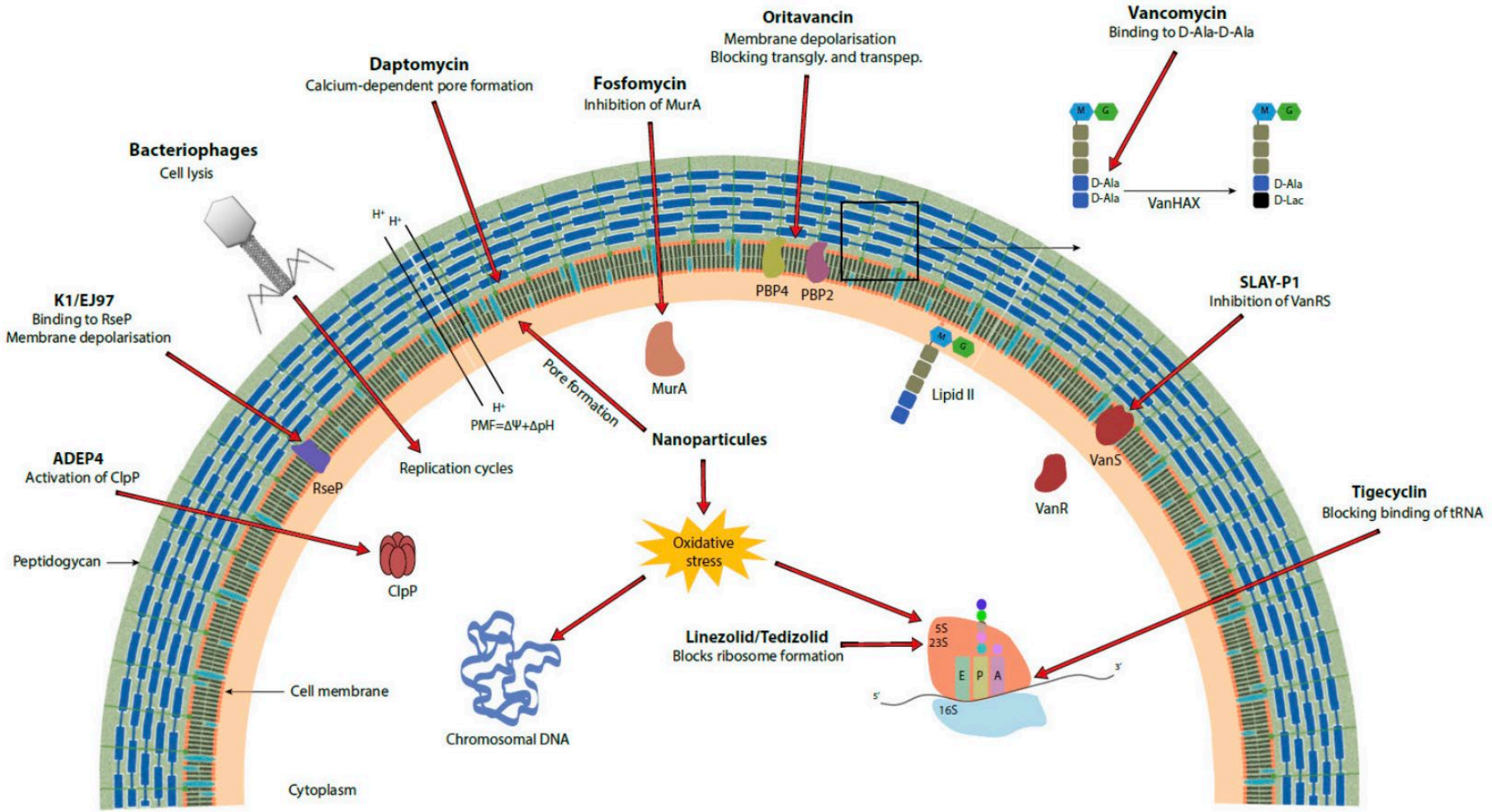
Consultant/Advisory Board/Speaker fees

- Pfizer, MSD, Angelini
- Thermo Fisher, Shionogi
- BioTest, Nordic Pharma, InfectoPharma
- Gilead Sciences, GSK
- Hikma, Advanz

- **Research grant**
  - Pfizer, MSD, Shionogi

Mechanism of Action of the Different Traditional & Non-traditional Strategies against Vancomycin-resistant Gram-positive Pathogens

Baetz B et al Antibiotics (Basel) 2021



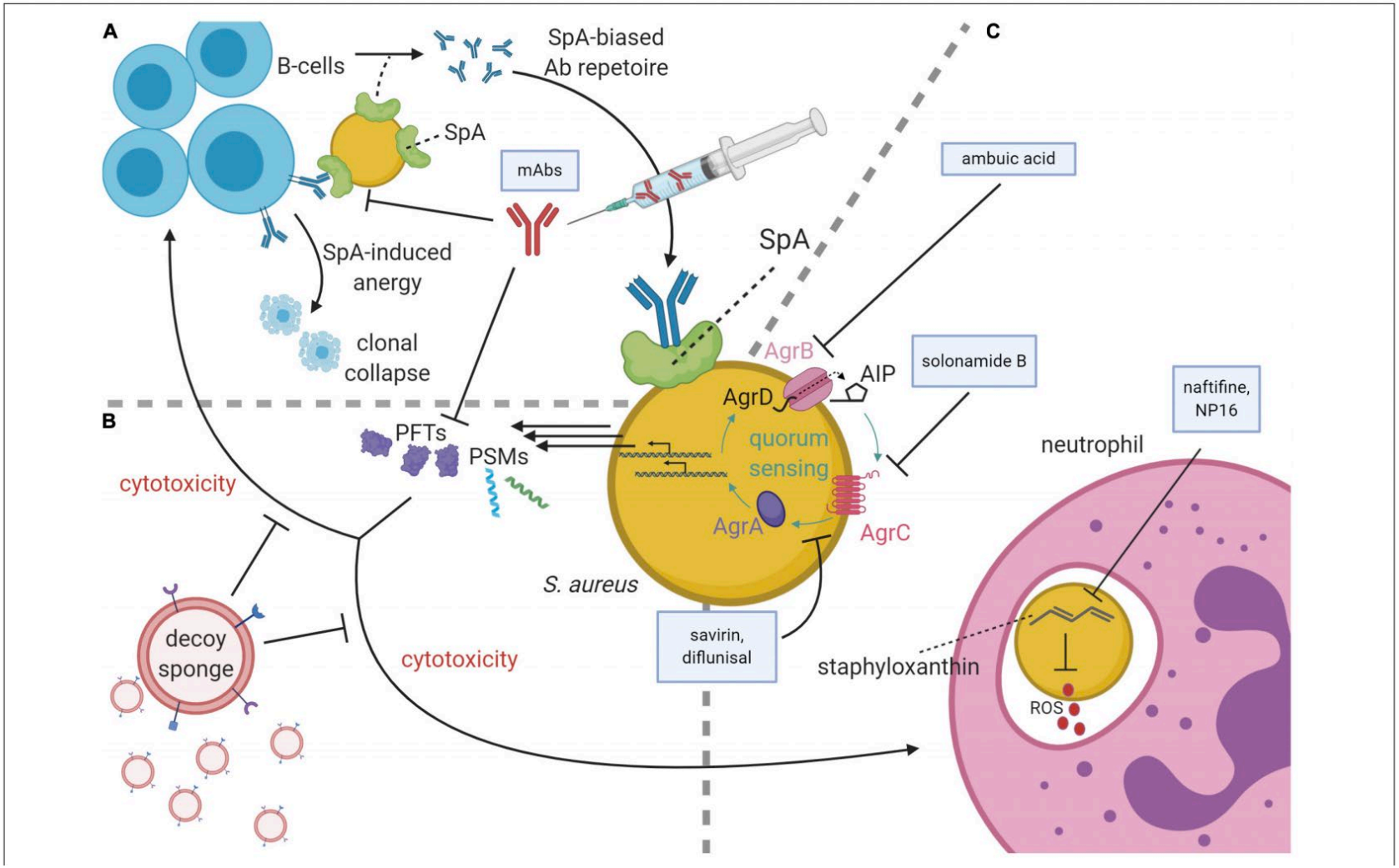
Mechanism of Action of the Different Traditional & Non-traditional Strategies against Vancomycin-resistant Gram-positive Pathogens

Baetz B et al Antibiotics (Basel) 2021

- Antimicrobial peptides
- Bacteriocins
- Lysins
- Nanoparticles

Antivirulence Strategies for *S. aureus* Infections

Ford CA et al Frontiers in Microbiology 2021

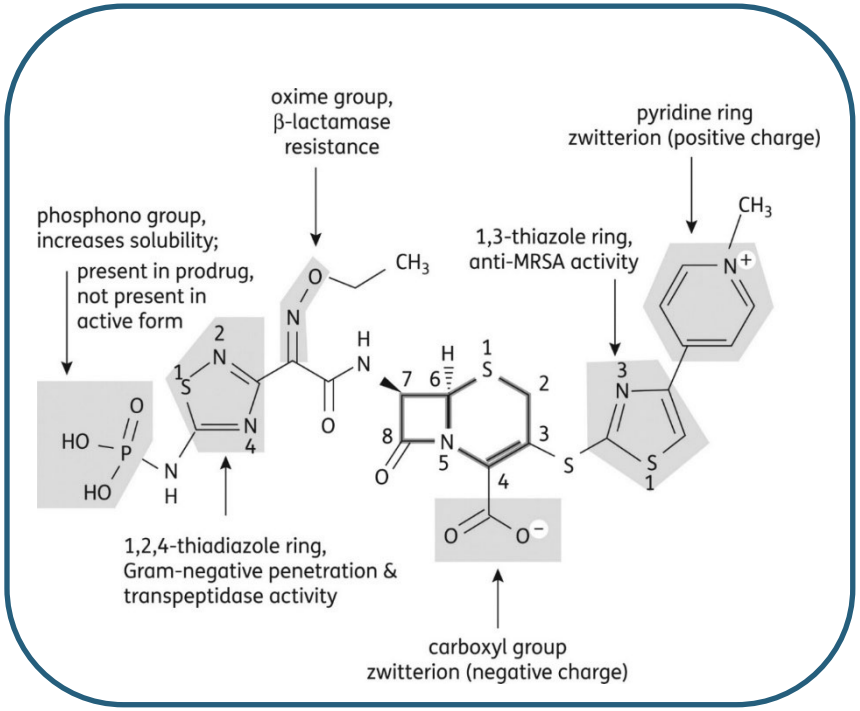


Ceftaroline fosamil

- First new drug in the IDSA 10 x '20 initiative[1]
- Parenteral, bactericidal, advanced/5th generation cephalosporin
- High affinity to specific penicillin-binding proteins associated with β-lactam resistance (altered PBPs) in *Streptococcus pneumoniae*[2]
- Anti-MRSA activity for cSSTI along with activity against other regular Gram-positive and Gram-negative bacteria[1]
- CLSI designates ceftaroline fosamil as a member of a new class of β-lactam antibiotic, 'cephalosporin with MRSA activity'

First MRSA-active β-lactam with tailored spectrum against common Gram-positive and Gram-negative bacteria[1]

Ceftaroline fosamil: Structure activity relationships[3]



CLSI, Clinical and Laboratory Standards Institute; IDSA, Infectious Diseases Society of America; MRSA, methicillin-resistant *Staphylococcus aureus*.

1. Goodman JJ and Martin SI. Ther Clin Risk Manag 2012;8:149–56; 2. Shorr AF, et al. *Diagn Microbiol Infect Dis*. 2013 Mar;75(3):298–303; 3. Zhanel GG, et al. Drugs 2009;69:809–31.

Ceftobiprole Perspective: Current and Potential Future Indications

Lupia T et al Antibiotics (Basel) 2021;10(2):170

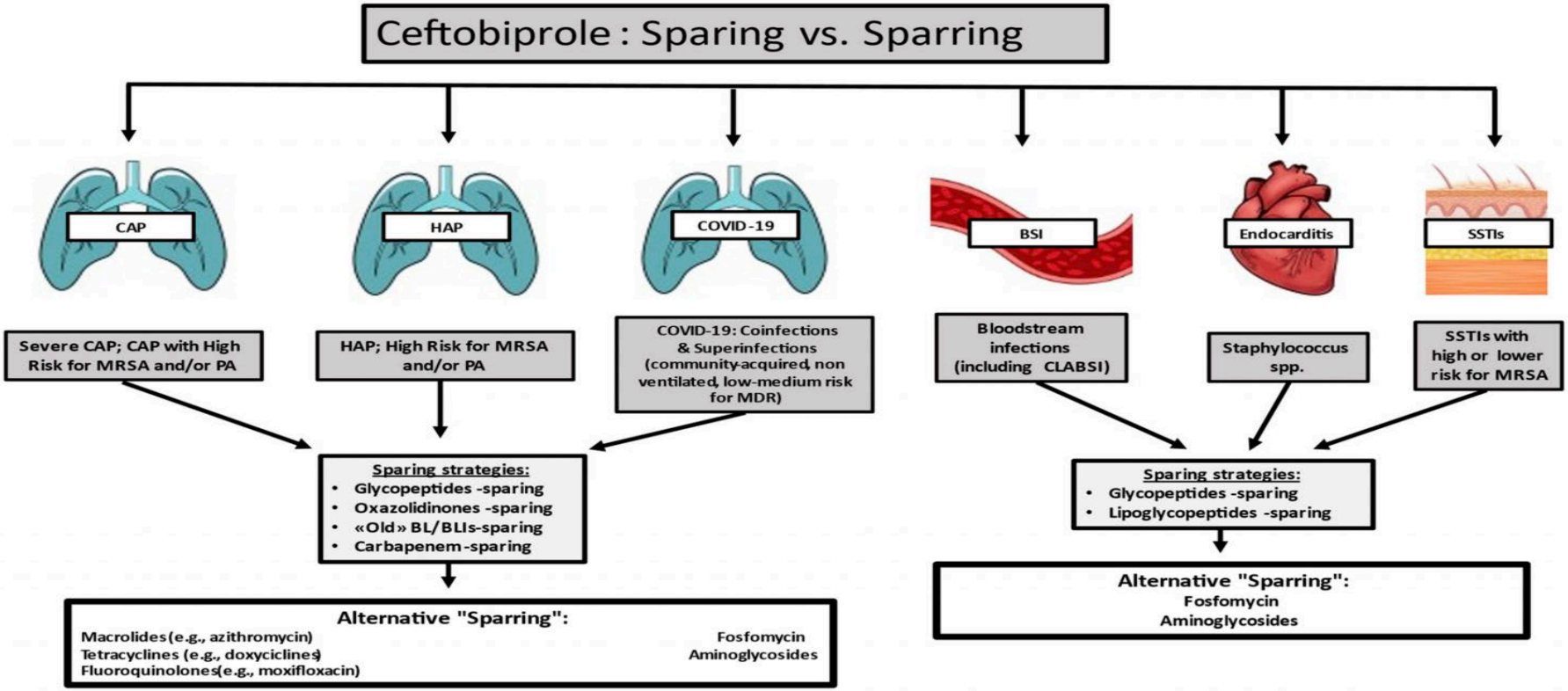


Figure 1. Ceftobiprole stewardship perspective: sparing vs. sparring. Abbreviations: CAP—community-acquired pneumonia; MRSA—methicillin-resistant *Staphylococcus aureus*; PA—*Pseudomonas aeruginosa*; HAP—hospital-acquired pneumonia; CLABSI—central-line associated bloodstream infections; BL/BLI—β-lactams/β-lactam inhibitor; SSTIs—skin and soft tissue infections.

Omadacycline for CAP

- **Omadacycline, a new once-daily aminomethylcycline antibiotic agent**
  - Iv & oral od formulation
- **Double-blind, 1:1 randomized trial, CAP PORT class II, III, or IV**
  - Noninferiority margin of 10 percentage points
  - Omadacycline 100 mg iv q12h for two doses, then 100 mg iv q24h
  - Moxifloxacin 400 mg iv q24h
  - Oral transition after 3 days
    - Oral omadacycline 300 mg q24h or Moxifloxacin 400 mg q24h
    - Total treatment duration was 7 to 14 days
- **Primary end point: Early clinical response**
  - Survival with **improvement in >2** of cough, sputum production, pleuritic chest pain, and dyspnea & **no worsening of symptoms** 72-120 hours & **no rescue antibacterial therapy**
- **Secondary end point:**
  - Investigator-assessed clinical response, 5 to 10 days after the last dose
  - Clinical response defined as resolution or improvement in signs or symptoms to the extent that further antibacterial therapy was unnecessary

Stets R et al NEJM 2019;380(6):517-527

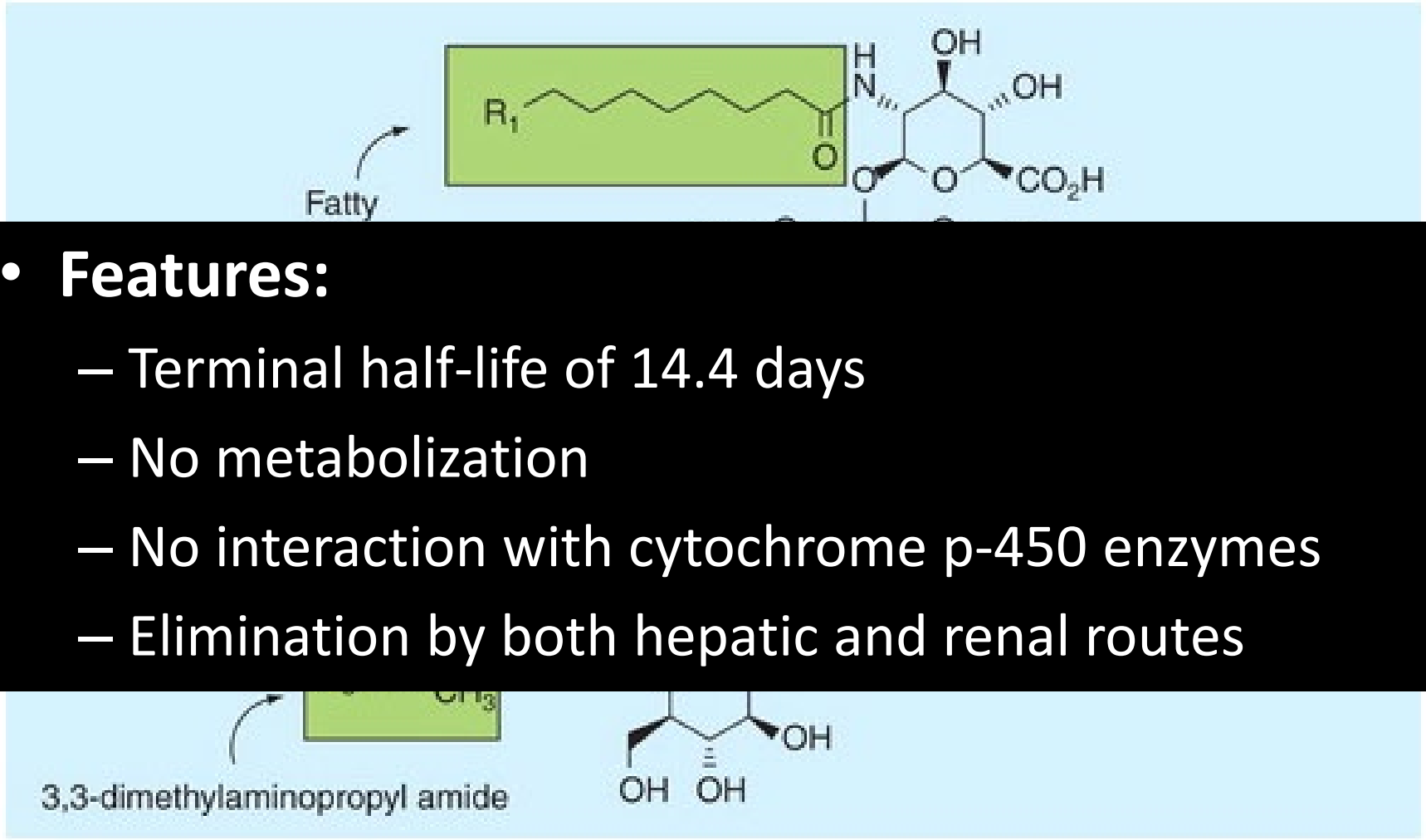
Omadacycline for CAP

- **Intention-to-treat population**
  - **386 patients (Omada) Vs. 388 patients (Moxi)**
  - **Non-inferiority demonstrated:**
  - **Early clinical response:**
    - 81.1% & 82.7%, respectively; diff, -1.6 percentage points; 95% CI,-7.1 to 3.8
  - **Investigator-assessed clinical response at the post-treatment evaluation**
    - 87.6% and 85.1%, respectively; difference, 2.5 percentage points; 95% CI, -2.4 to 7.4
- **Adverse events TEAEs (Omada Vs. moxi)**
  - **41.1% Vs. 48.5% of the patients**
  - **Gastrointestinal: 10.2% & 18.0%**
  - **Diarrhea: 1% & 8%**
  - **Deaths: 8 Vs. 4**
- **→ Omadacycline non-inferior to moxifloxacin**

Stets R et al NEJM 2019;380(6):517-527

Dalbavancin

Dunne MW et al Drug Saf 2015



- **Features:**
  - Terminal half-life of 14.4 days
  - No metabolization
  - No interaction with cytochrome p-450 enzymes
  - Elimination by both hepatic and renal routes

Tedizolid

Salavert Lletí M et al Rev Esp Quimioter 2021;34 S1:22-25

Table 1 Summary of new evidence for long-term treatments with tedizolid

Author (year, N)	Age (median, in years)	Linezolid (previous use,%)	BJI (%)	Duration of tedizolid therapy (days, interval)	Adverse events (%)	Discontinuation (%)	Cure or improvement (%)
Mensa et al., 2020; N=81	66	44%	47%	28 (14-59)	11%	5%	80%
York et al., 2020; N=60	62	82%	85%	27 (22-32)	GI: 15% fatigue: 12% anaemia: 2%	18%	72%
Benavent et al., 2021; N=51	65	16%	100%	29 (15-44)	5.8% (only GI)	0	83%
Senneville et al., 2020; N=33	73	9%	100% (PJI)	56 (42-84)	60% anaemia: 12% pruritus:12%	12%	82%

BJI: bone and joint infections; GI: gastrointestinal; N: number of patients /cases; PJI: prosthetic joint infections

Long-Term Tedizolid in Ostearticular Infections

Salavert Lletí M et al Rev Esp Quimioter 2021;34 S1:22-25

- **Multicenter retrospective study from Spain**
  - Long-term use effective
  - Better safety profile
  - Less myelotoxicity and lower drug-drug interactions than linezolid
- **Cases (n = 51)**
  - Osteoarthritis 53%
  - Prosthetic joint infection 33%
  - Diabetic foot infections 18%
- **65% of the isolates: Staphylococci**
  - *S. aureus* 48%
- **Reasons for choosing tedizolid**
  - Potential drug-drug interactions 63%
  - Cytopenia 55%
- **Median treatment duration** 29 days
- **Concomitant rifampin** 24%

Benavent E et al. Antibiotics (Basel) 2021; 101(1):5

Intravenous Fosfomycin: Systematic Review and Metanalysis

Grabein B et al. Clin microbiol Infect 2017; 363-372

- **Excellent efficacy against *S. aureus*, even in monotherapy**
- **Well-tolerated drug**
- **Favourable safety profile**
  - Serious adverse events being reported very infrequently
  - Adverse events generally mild, not requiring discontinuation of treatment
  - Manageable hypernatraemia and/or hypokalaemia

Fosfomycin: Old is New Again

Internal Medicine Journal 2018;48:1425-29

Table 1 Spectrum of fosfomycin activity

	Organism	Susceptibility
Gram positive	*Staphylococcus* spp.	
	Enterococcus faecalis	
	Enterococcus faecium	
Gram negative	*Escherichia coli*	
	Klebsiella spp.	
	Acinetobacter spp.	
	Pseudomonas aeruginosa	
	Citrobacter species	
	Proteus spp.	
	Providencia spp.	
	Bacteroides fragilis	

Highly susceptible (■). Moderately susceptible (■). Poor activity (■).

Beta lactams plus Daptomycin Combination Therapy for Infective Endocarditis: An Italian National Survey (BADAS)

Silvia Corcione, Tommaso Lupia , Carlo Pallotto , Daniele Roberto Giacobbe, Ilaria De Benedetto , Giacomo Stroffolini, Simone Mornese Pinna, Carlo Tascini, Matteo Bassetti and Francesco Giuseppe De Rosa, on behalf of SITA GIOVANI (Young Investigators Group of the SocietàItaliana Terapia Antinfettiva)

55 clinicians

12 italian regions

Empiric Daptomycin in IE	IE MRSA	IE MSSA	IE Enterococcus	IE Streptococcus
(Responding 52/55 partecipants)	47 (90.38)	2 (3.85)	3 (5.77)	0 (0)
Ongoing Resistant Streptococcus spp. strains to Daptomycin	**No**	**Yes**		
(Responding 52/55 partecipants)	40 (76.92)	12 (23.07)		
Monotherapy		11 (91.66)		
Combination		1 (8.34)		
Daptomycin in Clinical Practice in IE	**First-line in Empiric Therapy**	**First-line in MRSA IE**	**No First-line**	
(Responding 53/55 partecipants)	17 (31.48)	24 (44.44)	12 (24.07)	
Daptomycin Empirical in IE (Native Valve)				
High Clinical Efficacy	10 (18.87)			
Combination with AG-sparing	13 (24.53)			
High penetration in vegetations	6 (11.32)			
Safety and low toxicity	3 (5.66)			
Single-day administration and OPAT choice	3 (5.66)			
Biofilm acitivity	5 (9.43)			
High bacterial killing rate	13 (24.53)			
Low rate of resistant strains/favourable MICs	0 (0)			
Daptomycin Empirical in IE (Prostethic Valve)				
High Clinical Efficacy	5 (9.80)			
Combination with AG-sparing	5 (9.80)			
High penetration in vegetations	4 (7.84)			
Safety and low toxicity	5 (9.80)			
Single-day administration and OPAT choice	1 (1.96)			
Biofilm acitivity	29 (56.86)			
High bacterial killing rate	2 (3.92)			
Low rate of resistant strains/favourable MICs	0 (0)			
Daptomycin dose in clinical practice in IE				
(≤6 mg/kg) Monotherapy	0 (0)			
(≤6 mg/kg) Combination	4 (7.41)			
(8-10 mg/kg) Monotherapy	12 (22.22)			
(8-10 mg/kg) Combination	38 (70.37)			
Daptomycin in combination therapy in IE				
Rifampin	5 (10.42)			
AG	4 (8.33)			
Beta-lactams	26 (54.17)			
Cephalosporins (III or IV gen)	4 (8.33)			
Novel Cephalosporins	9 (18.75)			

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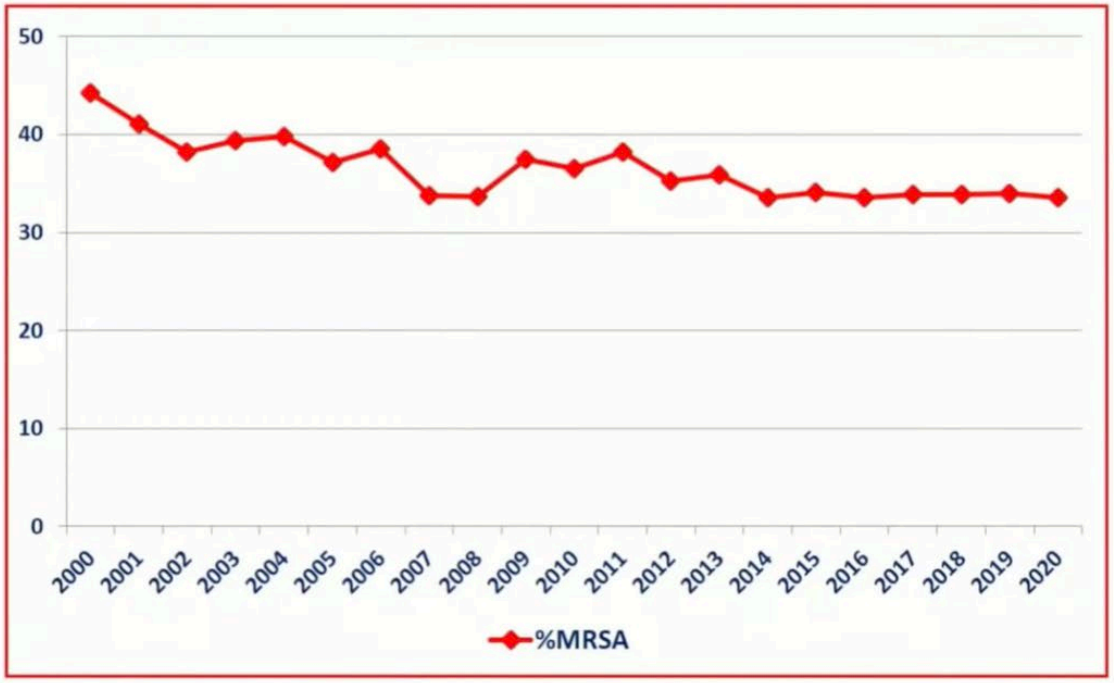
Daptomycin plus Beta-lactams in IE		
Streptococcus spp	0 (0)	
MSSA	2 (3.70)	
MRSA	25 (46.30)	
Both MRSA and MSSA	10 (18.52)	
Enterococcus spp	10 (18.52)	
Indipendently to pathogens	7 (12.96)	
Daptomycin plus Beta-lactams in IE (regimens)		
Empiric therapy	9 (16.98)	
Targeted plus OPAT	14 (26.42)	
Targeted then oral de-escalation	19 (35.85)	
Targeted in-hospital (no OPAT)	11 (20.75)	
De-escalation after Daptomycin therapy in IE (stable/operated)		
After 1-2 wks	22 (40.00)	
After 3 wks	18 (32.73)	
After 6 wks	3 (5.45)	
De-escalation is not common in our centre	12 (21.82)	
Choices for De-escalation after Daptomycin in IE	**MSSA**	**MRSA**
	Beta-lactams	*TMP/SMX*
	Cephalosporins	*Dalbavancin*
	TMP/SMX	*Linezolid*
	Clyndamicin	*Doxicycline*
	Doxicycline	*Rifampicin*
	Rifampicin	
	Fluoroquinolones	
Daptomycin interruption or substitution		
Partial or no response	*1 (1.85)*	
Adverse effects	*7 (12.96)*	
Costs	*3 (5.56)*	
Medications more accessible in OPAT or long-term facility	*23 (42.59)*	
De-escalation	*20 (37.04)*	

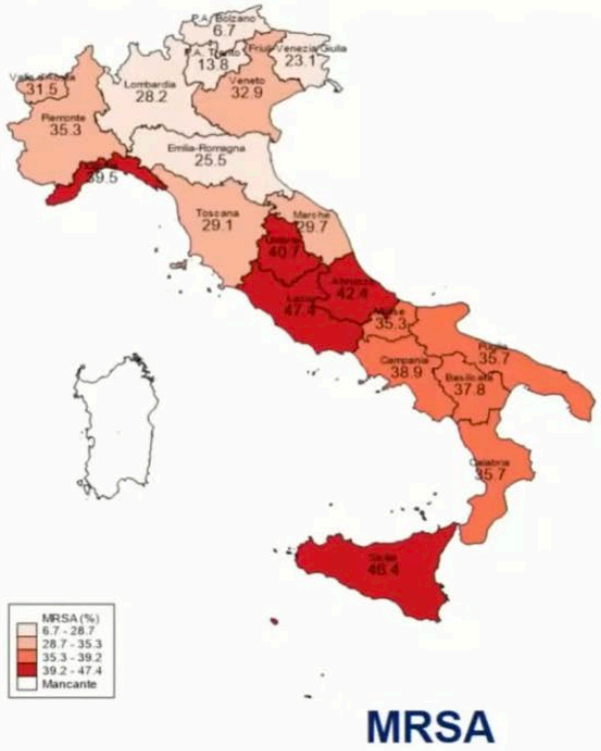
Dati AR-ISS 2020

Staphylococcus aureus resistente alla meticillina (MRSA)

Trend 2000-2020



Prevalenza Regionale 2020



Dati AR-ISS 2020

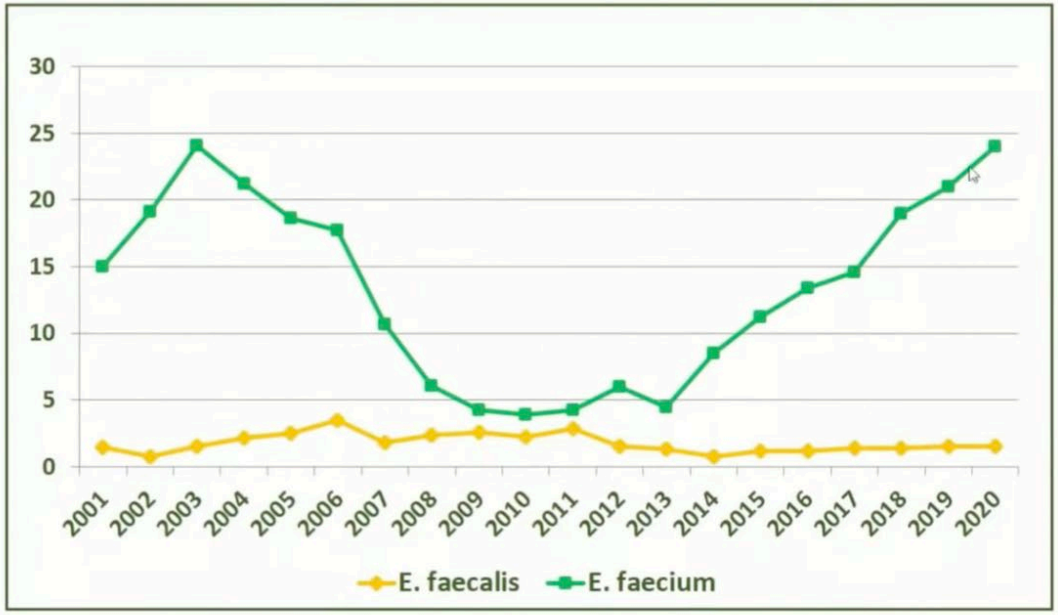
DIPARTIMENTO MALATTIE INFETTIVE

Enterococchi

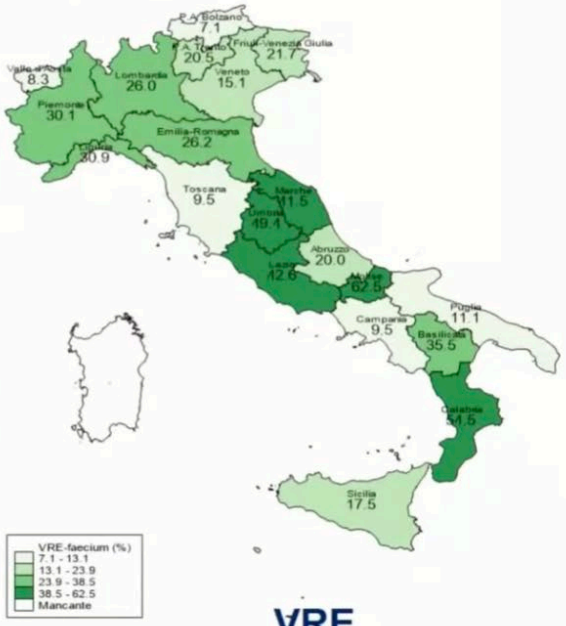
Resistenza alla vancomicina (VRE)

% VRE

Trend 2001-2020



Prevalenza Regionale 2020



VRE

Mechanism of Action of the Different Traditional & Non-traditional Strategies against Vancomycin-resistant Gram-positive Pathogens

Baetz B et al Antibiotics (Basel) 2021

- **VanA and VanB resistance operons are the most widespread**
  → Modification of the dipeptide D-Ala-D-Ala to D-Ala-D-Lactate
- **VanA type**
  - Control by VanR/VanS two component system
    - VanS activated by vanco & teico
- **VanB type**
  - Control by VanRB/VanSB two component system
    - VanSB activated only by vanco
- **Epidemiology of VR *E. faecium***
  - 2014 — 10% of Enterococcal isolates
  - 2019 — 18% of Enterococcal isolates
  - ECDC, EARSNet, 2020
  - ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2019
- **Mortality of bacteremia**
  - 2.5 times higher with VRE as compared to VSE
    - DiazGranados CA et al 2005; 41: 327-333

Daptomycin against Enterococci

Baetz B et al Antibiotics (Basel) 2021

- **Higher mortality than linezolid in bacteremias**
  - Chuang YC et al JAC 2015
- **Still active Vs. VRE and probably preferable in some infections such as infective endocarditis**
  - O'Driscoll T et al Infect Drug Resist 2015; 8: 217-230
- **Non-Susceptible strains: 1% worldwide 20,39**
  - Werth BJ et al JAC 2015
  - Bender JK et al Drug resist Updates 2018; 40: 25-39
- **REsistance: different in *E. faecalis* Vs. *E. faecium***

Iclaprim

September 26, 2019 Clinical Trials Gov

- **Dihydrofolate reductase inhibitor: Phase III clinical development:**
  - ABSSSI
    - REVIVE 1-2 → completed, results available
    - Iclaprim (80 mg q12h iv) non-inferior to dose-adjusted vanco
  - cSSTI:
    - ASSIST 1-2 → completed
  - HAP, HCAP, VAP
    - Vs. Vanco → terminated, no results
    - Two different results of iclaprim q12h
- **HAP:**
  - Additional studies planned
- **Iclaprim → New alternative for Gram-positive ABSSSIs**

Huang DB & Dryden M. Future Microbiol 2018;13:957-969

Iclaprim Vs. Vanco in ABSSSIs: A Pooled Analysis of the Phase 3 REVIVE 1-2 Trials

Noviello S et al. J Med Microbiol. 2020;69(4):625-630

- 602 patients from REVIVE 1-2

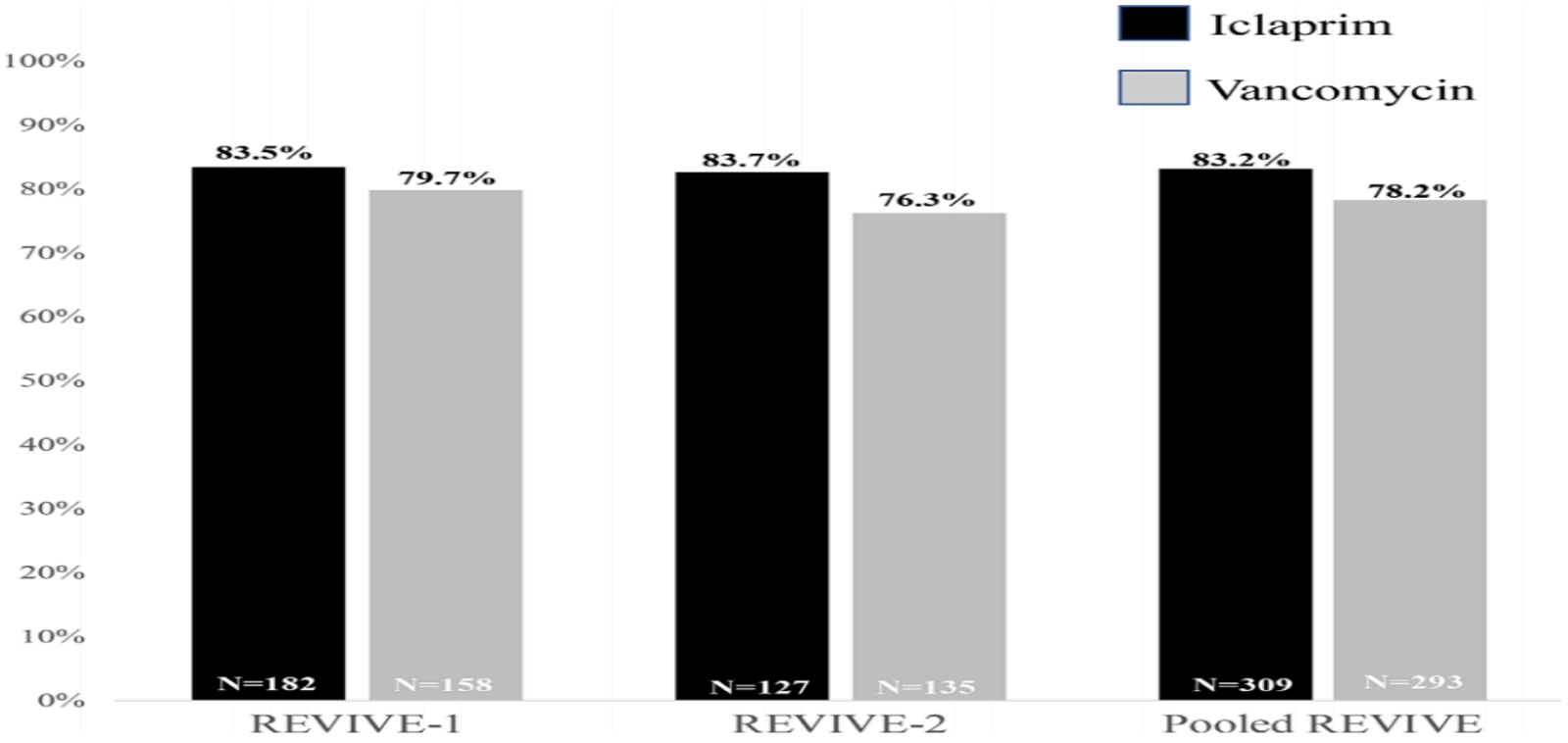


Fig. 2. Early clinical response at the early time point for iclaprim and vancomycin arms in patients with wound infections in the REVIVE studies.

Lefamulin: Promising Novel Pleuromutilin Antibiotic

Veve MP & Wagner JL Pharmacotherapy 2018 Sep;38(9):935-946

- **Pleuromutilin developed in 1950**
- **Time-dependent killing**
- **Microbiological activity**
  - Gram-positive and atypical organisms associated with CABP
    - *S. pneumoniae, Haemophilus influenzae, Mycoplasma pneumoniae*
    - *Legionella pneumophila*, *Chlamydophila pneumoniae*
  - *Staphylococcus aureus*
    - MRSA, VISA, heterogeneous strains
  - Vancomycin-resistant *E. faecium*
  - Activity against
    - MDR *Neisseria gonorrhoeae*
    - *Mycoplasma genitalium*

Lefamulin
ID Exchange 21 August 2019

- **FDA Approves Lefamulin For CAP**
  - Two studies Vs. moxifloxacin (+/- Linezolid) com
    - Clintrialsgov → trials completed
  - Interference with the bacteria's ability to replicate
  - Available in both injectable (IV) and oral forms
- Reuters (8/19, Joseph, Sarkar)
  - FDA approved Nabriva Therapeutics Plc's Xenleta (lefamulin) "for treating patients with CAP
- MedPage Today (8/19, Walker) also covers the story

Lefamulin Efficacy and Safety in a Pooled phase 3 CAP Studies and Common Clinical Comorbidities (LEAP)

File TM Jr et al. BMC Pulm Med. 2021;21(1):154

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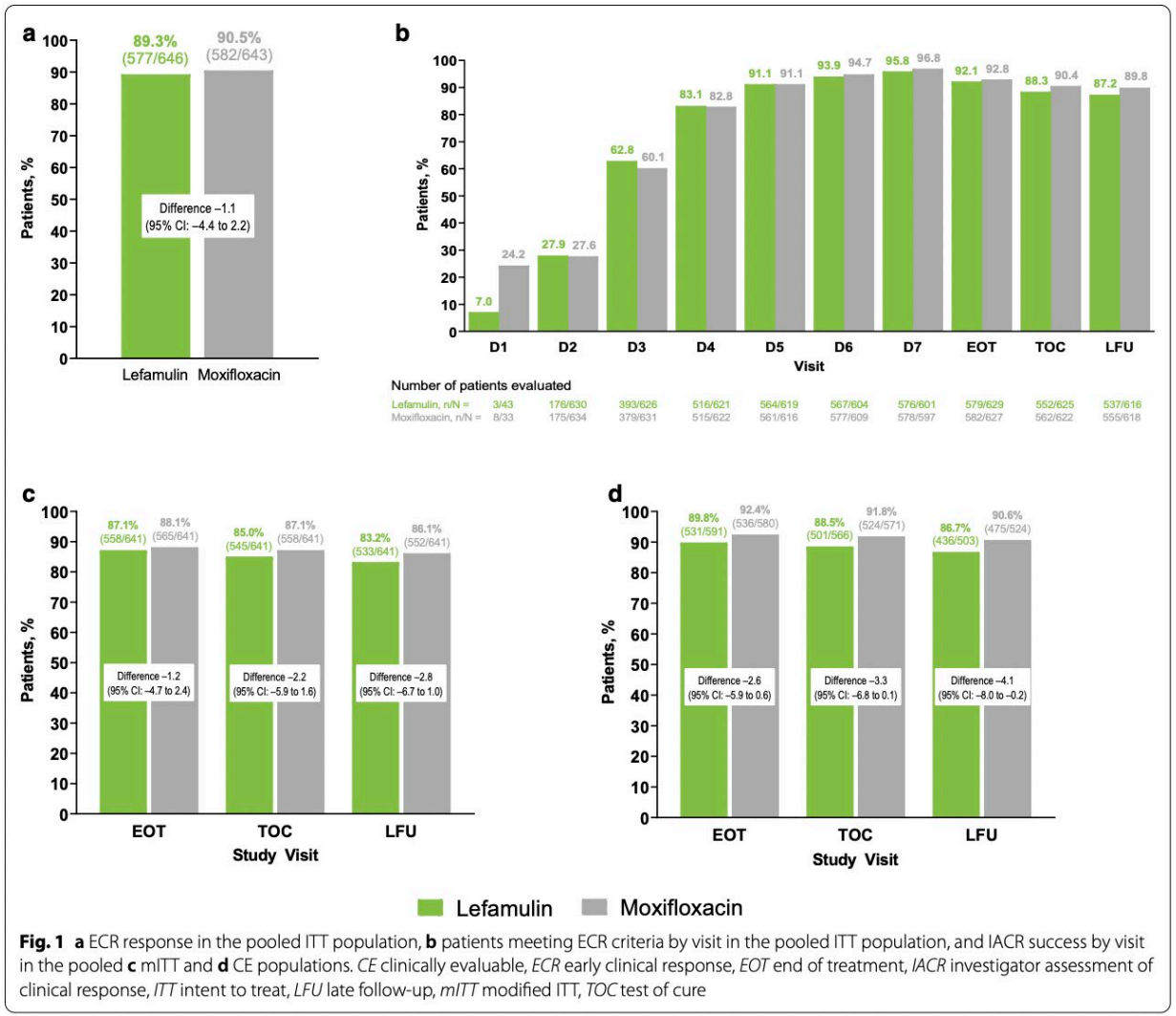

Fig. 1 **a** ECR response in the pooled ITT population, **b** patients meeting ECR criteria by visit in the pooled ITT population, and IACR success by visit in the pooled **c** mITT and **d** CE populations. *CE* clinically evaluable, *ECR* early clinical response, *EOT* end of treatment, *IACR* investigator assessment of clinical response, *ITT* intent to treat, *LFU* late follow-up, *mITT* modified ITT, *TOC* test of cure

Lefamulina

Dosaggio	**Durata del trattamento**
Esclusivamente lefamulina per via orale: 1 compressa di Xenleta da 600 mg per via orale ogni 12 ore	5 giorni
Lefamulina per via endovenosa con l'opzione di passare alla formulazione orale: 150 mg di Xenleta ogni 12 ore mediante infusione endovenosa nell'arco di 60 minuti con l'opzione di passare alla compressa di Xenleta da 600 mg da assumere per via orale ogni 12 ore	trattamento totale di 7 giorni, mediante via endovenosa o mediante combinazione della via endovenosa e orale

Conclusioni

- **Revival**
  - Fosfomicina, daptomicina
- **Varietà di classi ed indicazioni**
- **Anche long-life o lineless antibiotics**
  - Dalbavancina
- **Monoterapia e Combinazione**
- **Efficacia delle nuove classi in real-life**
- **Grande attività di stewardship**