Infezioni da Gram-positivi Difficili: Opzioni Diverse per Diversi Settings

Genova 22 Giugno 2022

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

Agenti Etiologici

- **MSSA / MRSA**
- **Stafilococchi coagulasi-negativi**
- **Enterococchi**
  - *E. faecalis* Vs. *E. faecium*
  - VSE / VRE
- ***Clostridioides difficile***
  - .....

Post-operative Abdominal Infections: Epidemiology, Operational Definitions, and Outcomes

Bassetti M et al. Intensive Care Med 2019

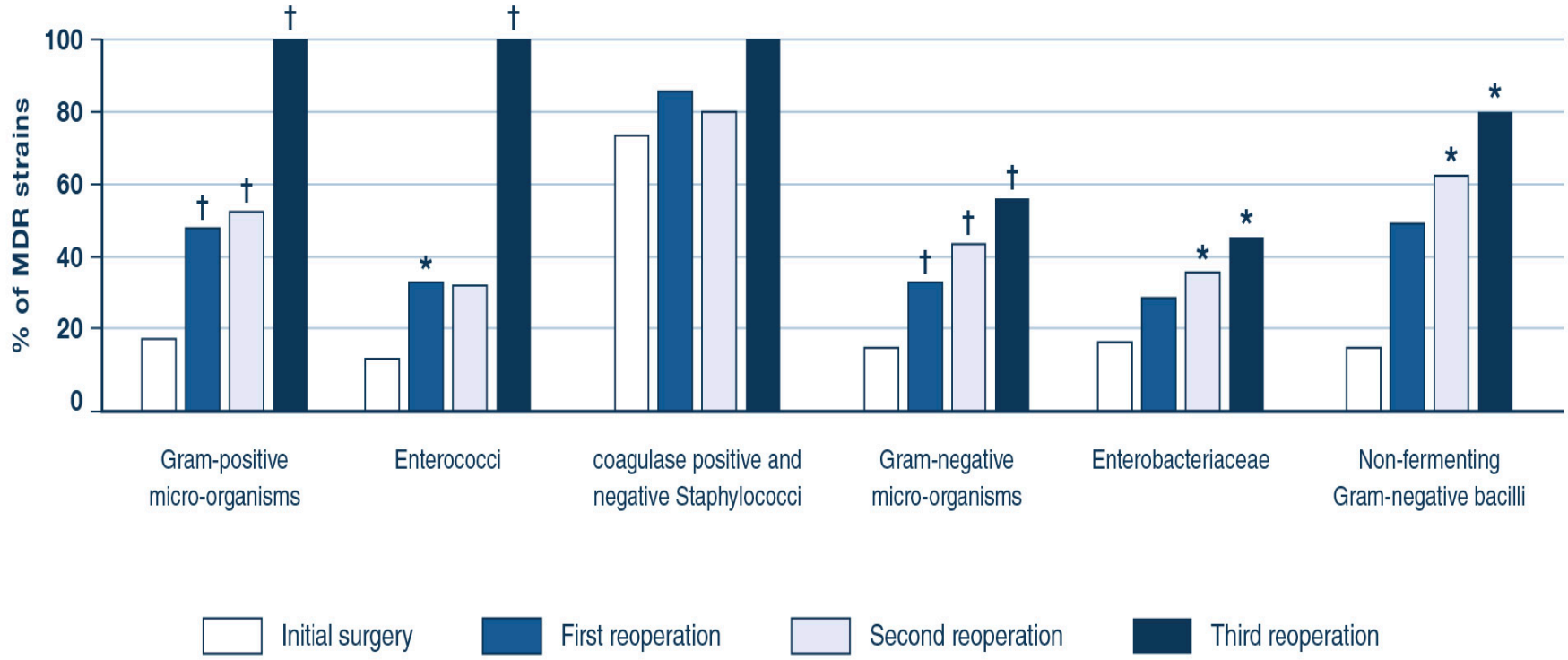


Fig. 1 The emergence of multi-drug resistant (MDR) bacteria is expressed as proportions of the respective species obtained from surgical samples at the time of initial surgery and first, second and third reoperation (adapted from [14]). *$P < 0.05$, †$P < 0.01$ versus initial surgery

Enterococcal Infections

Krawczyk B et al Microorganisms 2021

- **Bacterial factors favoring:**
  - Colonization & aggregation into the extracellular matrix
- **Migration of bacteria**
  - Aggregatory substances, polysaccarides, Epa antigen
- **Translocation into lymphonodes, blood, liver, spleen**
- **Sepsis and infective endocarditis**
- ***E. gallinarum* can cause autoimmune diseases in genetically predisposed hosts**
  - Pathobiontic: pathogenic bacteria from microbiota

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

Dati AR-ISS 2020

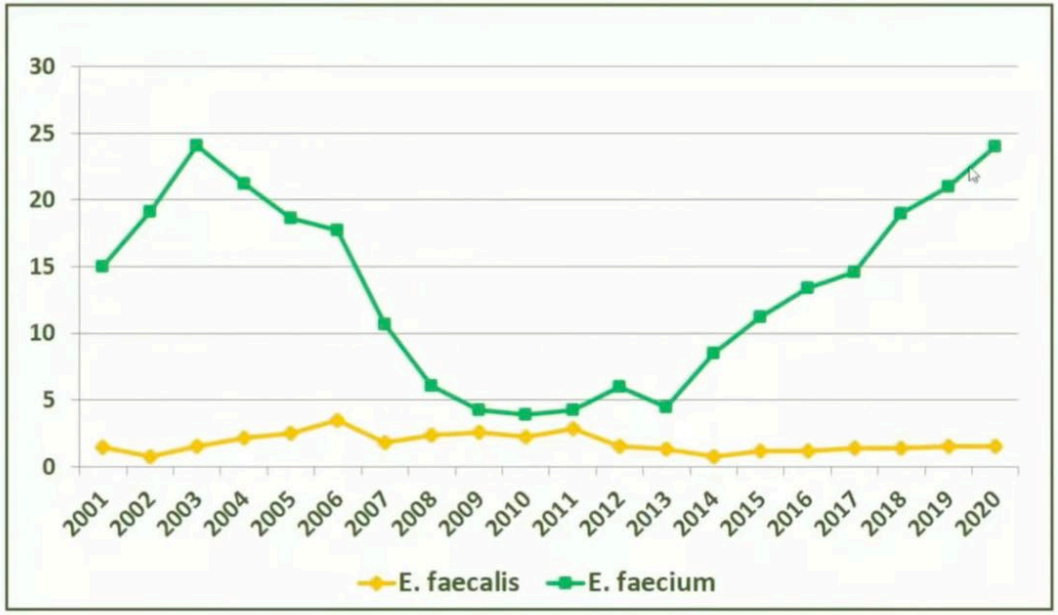
DIPARTIMENTO MALATTIE INFETTIVE

Enterococchi

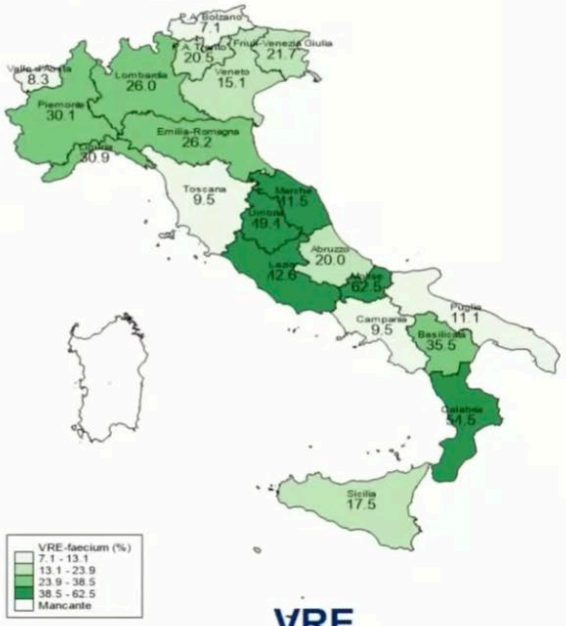
Resistenza alla vancomicina (VRE)

% VRE

Trend 2001-2020



Prevalenza Regionale 2020



VRE

High-Dose Daptomycin and Clinical Applications
Jones TW et al Ann Pharmacother 2021 Feb

- **High-dose daptomycin**
  - Salvage and first-line therapy for endocarditis and bacteremia, primarily when caused by MRSA and Enterococcus
  - Effective for osteomyelitis and central nervous system infections, although comparative studies are lacking
  - In renal replacement therapy requires considering clearance modality to achieve exposures like normal renal function
- **Obesity:**
  - Weight-based dosing draws concern for elevated exposures, although high doses have not been evaluated kinetically in obesity
  - Some data show benefits of high doses in overweight populations
- **Burn patients**
  - More rapid clearance, and high doses may only achieve drug exposures similar to standard doses (6 mg/kg)

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**
  - 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***

New Perspectives on Antimicrobial Agents: Long-Acting Lipoglycopeptides

Tran TT et al AAC 2022

- Microbiology
- Vanco as a surrogate marker of sensitivity
- PK
- Combination treatment
- Resistance issues
- Real-world experiences

New Perspectives on Antimicrobial Agents: Long-Acting Lipoglycopeptides

Tran TT et al AAC 2022 (& REFF 7-9-10-11)

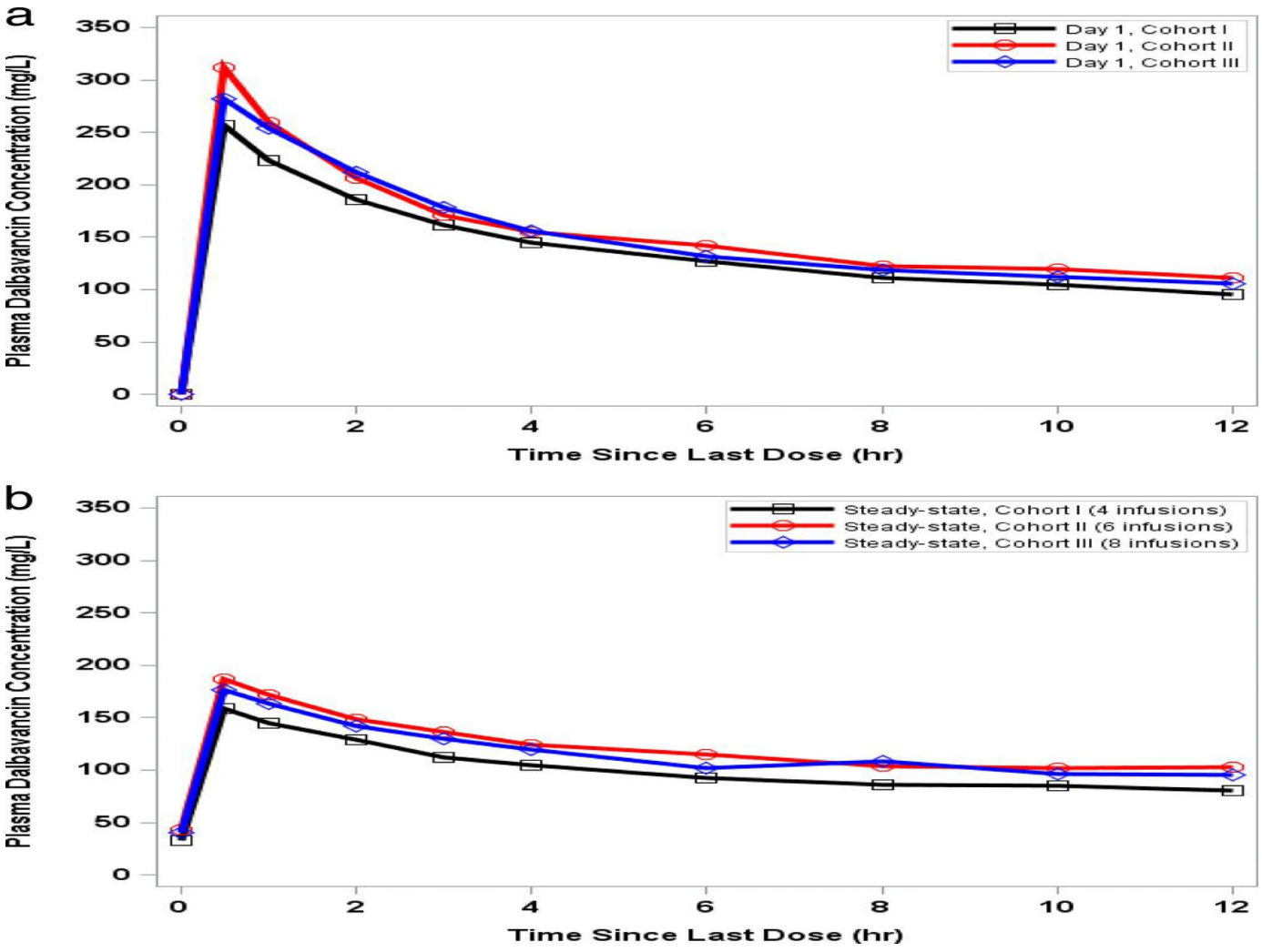
- **Broth dilution should be the reference method**
- **Susceptibility breakpoints for Dalbavancin:**
  - **CLSI breakpoints:** staphylococci, streptococci, and enterococci: ≤0.25
  - **EUCAST breakpoints:** staphylococci and streptococci equivalent: ≤0.125 mg/L
- **Susceptibility breakpoints for Oritavancin**
  - **CLSI breakpoints:** staphylococci, streptococci, and enterococci
    ≤0.12, ≤0.25, and ≤0.12 mg/L, respectively
  - **EUCAST breakpoints:** *Staphylococcus aureus* and streptococci
    ≤0.125 and ≤0.25 mg/L respectively
- **MIC50/MIC90 literature reference**
  - Oritavancin: 0.03/0.06, 0.03/0.12, 0.008/0.008, and 0.015/0.06 mg/L, respectively for staphylococci, streptococci, vancomycin-susceptible enterococci (VSE), and VRE
  - Dalbavancin: 0.03/0.03, 0.008/0.03, and 0.03/0.12 mg/L, respectively for staphylococci, streptococci, enterococci are

Vancomycin: Surrogate Marker for LGPs Sensitivity (Dalba & Orita)

Tran TT et al AAC 2022

- **EUCAST considerations**
  - Feasibility of vanco surrogacy
  - Not CLSI
- **Potential drawbacks:**
  - hVISA, VRE, CoNS
- **97% concordancy**
  - Beta-haemolytic streptococci and vanco-susceptible Enterococci
- **Nonsusceptible test result with gradient diffusion, BMD**
  - Should always be repeated
  - All reproducible nonsusceptible isolates → reference laboratory
- **Wide availability of testing with commercial platforms**

Mean Dalbavancin Plasma Concentrations
Day 1 (a) & Steady State (b)



Michael W. Dunne et al. AAC 2015;59:1849-1855

Oritavancin

Hoover RK et al Open Forum Infect Dis 2022

- **Bactericidal Vs. MSSA, MRSA, streptococci, VRSA**
  - Multiple mechanisms Vs. VRE
- **Disruption of Gram-positive membrane integrity**
  - → Depolarization, permeabilization & rapid cell death
  - → Distinct mechanism from daptomycin
  - → Still active Vs. dapto-R strains
- **Inhibition of the transglycosylation step**
  - Binding the D-Ala-D-Ala as glyco- & lipopeptides
- **Inhibition of the transpeptidation step**
  - Active Vs VRE & VRSA

References 14-25 from above

Oritavancin Vs. *C. difficile*

Hoover RK et al Open Forum Infect Dis 2022

- More potent than vanco Vs. *C. difficile*
- Adheres to *C. difficile* endospores
- May prevent vegetative overgrowth

References 23-25 from above

Advantages of Outpatient Treatment with Long-Acting Lipoglycopeptides (laLGP)
Krsak M et al. Pharmacotherapy. 2020;40(5):469-478

- **Possible utility in transitions to outpatient settings:**
  - People who use drugs, those who cannot reliably adhere to unsupervised treatment (poor mental or physical health)
  - People with complicating life circumstances (e.g., homelessness, incarceration, rural location)
  - Inadequate health insurance
- **Review of evidence and possible cost-effectiveness from patient, payer, and hospital perspectives**
- **Barriers to broader use of laLGPs:**
  - Relative lack of prospective data regarding efficacy in serious infections
  - Narrow US & FDA indications restricted to ABSSSI
  - Lack of reimbursement infrastructure

Table 1. Colorado Protocol: Guide to Outpatient Transition Using Long-Acting Lipoglycopeptides

Step 1: Determine overall eligibility/suitability for laLGP therapy

- Adults ≥ 18 yrs of age, **AND**
- Presence of Gram-positive organism (vancomycin susceptible), **AND**

a Exception: VRE (oritavancin only), limited evidence, only indicated if limited/no other options

- Patient is a poor outpatient parenteral antimicrobial therapy (OPAT) candidate (e.g., PWUD, anticipated problems with adherence to other treatment options, homeless, complicating social circumstances, insurance coverage issues) **AND**
- Patient does not have CNS involvement with infection, **AND**
- Clinically stable and responding to appropriate treatment, **OR**

If additional doses are needed as an outpatient:

- Medicare will **NOT** pay for off-label use
- Approved ICD-10 codes for billing/consideration
- Cellulitis: L.03
- MRSA: A49.02 (unspecified site) and B95.62 (MRSA infection as cause of disease classified elsewhere)
- *Staphylococcus*: A41.01–A41.2 (sepsis due to *Staphylococcus*), A49.01 (MSSA unspecified site), B95.61–B95.8 (*S. aureus* as the cause of disease classified elsewhere)
- *Streptococcus*: A40.0–A40.9 (Streptococcal sepsis), A49.1 (Streptococcal infection unspecified site), B95.01–B95.1 and B95.3–B95.8 (*Streptococcus*)

Step 3: laLGP choice and dose at our institution – dalbavancin vs oritavancin

- Dalbavancin – 1500 mg IV infused over 30 min prior to discharge in patients with normal renal function[a,b] => preferred if the patient is likely to need additional doses in the outpatient setting (shorter infusion duration in comparison with oritavancin, though shorter infusions are currently studied in oritavancin as well[52,53]); also, the 2-dose regimen (1500 mg × 2 infusions total, 7 days apart) for osteomyelitis has been established prospectively
- Oritavancin – 1200 mg IV infused over 3 hrs prior to discharge in patients with normal renal function[a,b] => preferred over dalbavancin if the patient has confirmed or possible VRE.

laLGP = long-acting lipoglycopeptides; IV = intravenous; VRE = vancomycin-resistant enterococcus.

[a]Lower doses, 1000 mg for dalbavancin (or renal adjustment per dalbavancin package insert) and 800 mg for oritavancin, can be used in people with decreased renal function and/or people with advanced age.

[b]The decision regarding a desired dose for initial and dosing under normal circumstances and in cases of decreased renal function and/or advanced age should always be informed by a consultation between the ordering physician and a pharmacist.

Dalbavancin & Oritavancin: Currently Active Registered Clinical Trials

Tran TT et al AAC 2022

Drug and trial identifier	*n*	Infection(s)	Design	Dosing	Comparator	Primary outcome	Status	Comments
Oritavancin								
NCT03761953	15	*S. aureus* bacteremia with or without IE	Single-center, open-label, pilot study	1,200 mg once[b]	None	Relapse at 6 wk	Recruiting	Focused on opioid users, requires prove of negative blood cultures
Dalbavancin								
NCT03982030	24	Bacteremia, right-sided IE, BJIs	Phase 4, single-center, open-label, pilot study	1,500 mg on day 0 and days 8–10	None	Clinical success and relapse at 6 wk	Not yet recruiting	Excludes left-sided IE, requires prove of negative blood cultures.
NTC03426761	50	BJI, including PJI and septic arthritis	Phase 4, randomized, open-label, pilot study	1,500 mg on day 0 and every 14 days (2–4 times)	SOC	Clinical cure at 6 wk	Recruiting	Confirmed Gram positive on culture
NTC04775953	200	Complicated *S. aureus* bacteremia or right-sided native valve IE	Phase 2b, multicenter, randomized, open-label, assessor-blind, superiority study	1,500 mg on days 1 and 8	SOC	Clinical success (DOOR)	Recruiting	Patients must have cleared their baseline bacteremia
NTC05046860	43	Acute or chronic PJI of knee or hip (1st episode) due to *Staphylococcus* spp.	Single group, open label	1,500 mg on days 0, 15, and 36	None	Clinical success at 48 wk	Not yet recruiting	Patients will also receive rifampin 600 mg daily, all patients undergo surgical debridement with implant retention (acute infections) or 1-stage revision (chronic infections)
NTC05117398	406	Noncomplicated CR-BSI due to *S. aureus*	Phase 3, pragmatic, open-label, noninferiority, randomized multicenter trial	1,500 mg once	SOC	Clinical cure and relapse at day 30	Not yet recruiting	Catheter removal required before entering study

[a]BJI, bone and joint infection; BSI, bloodstream infection; CR, catheter-related; DOOR, desirability of outcome ranking; IE, infective endocarditis; PJI, prosthetic joint infection; SOC, standard of care. Information was obtained from www.clinicaltrials.gov. Only clinical studies with primary endpoints focusing on clinical outcomes were included.

[b]The aim is to complete the last 2 weeks of therapy out of a total of 4 weeks for bacteremia and 6 weeks for infective endocarditis.

UNIVERSITÀ
DEGLI STUDI
DI TORINO

Results I: population and PK

	Overall	*PK intensification: Group 0*	*Group 1*	*Group 2*	*Group 3*
Variable	Value (median/ %)	-	-	-	-
N. patients	71	17	9	13	2
Age	60 [50-70.5]	60 [51-73]	67 [48-75]	60 [48-71]	40 [17-40]
Ethnicity: caucasian	100%	-	-	-	-
Sex: Male	60%	53	75	60	50
Albumin	43 [40-45] g/L	44 [39-46]	44 [43-46]	43 [42-45]	45 [40-45]
BMI	24.5 [22.2-28.2]	26 [22-31]	20 [22-24]	24 [23-30]	23 [21-23]
BSA	1.7 [1.4-2.2]	1.8 [1.5-2.3]	1.6 [1.2-1.8]	1.9 [1.7-2.2]	1.2 [1-1.3]
eGFR	94.5 [77.3-116.2]	86 [74-104]	91 [79-126]	100 [73-118]	112 [90-113]
AEs	1%	1	-	-	-
Infection control	36 (47%)	60%	30%	80%	50%
Diabetes	19 (25%)	23%	13%	23%	-
Previous therapy	96 %	100	89	100	100
N. therapy lines (1)	75 %	67	50	40	50
Length therapy	14 [14-35] days	14 [14-56]	35 [23-75]	35 [28-105]	35 [14-35]
Reasons for DBV (failure)	44 %	53	55	31	50
Outcome (cure)	58/71 (82)%	14/17 (82%)	9/9	7/13	2/2
Time to cure	28 [28-56] days	14 [14-56]	84 [49-105]	84 [84-112]	28 [28-84]

UNIVERSITÀ DEGLI STUDI DI TORINO

Results I: population and PK

	Overall	*Group 0*	*Group 1*	*Group 2*	*Group 3*
Type of infection	ABSSSIs: 16 (21) LVAD: 3 (4) Endocarditis: 3 (4) OA: 54 (71): • Osteomyelitis: 13 (25) • Spondylodiscitis: 8 (15) • Septic arthritis: 5 (11) • PJI: 27 (49)	ABSSSIs: 7 LVAD: 2 Septic arthritis: 1 Osteomyelitis: 2 PJI: 5	Septic arthritis: 1 Osteomyelitis: 4 Spondylodiscitis: 3 Endocarditis: 1	ABSSSIs: 2 Septic arthritis: 1 Osteomyelitis: 3 Spondylodiscitis: 2 PJI: 5	Spondylodiscitis: 1 PJI: 1
Microorganisms	- MSSA: 32 (42%) - MRSA 23 (30) - MRSE 7 (9.2) - MSSE 2 (2.6) - *S. Lugdunensis 1 (1.3)* - *Streptococci:3 (4.1)*	- MRSA: 4 - MSSA: 8 - MRSE: 3	- MRSA: 3 - MSSA: 3 - MRSE: 1 - *Streptococcus dysgalactiae:*1	- MSSA:8 - MRSA: 4 - MSSE: 1	- MRSA: 2

PJI: Prosthetic joint infection

Combination Treatment

Tran TT et al AAC 2022

- **Oritavancin**
  - Linezolid, rifa, genta Vs. hVISA, VISA, VRSA
  - Genta Vs. VSE & *vanA*-type VRE
  - Other combinations inconsistent / variable
  - Possible antagonism: dapto, rifa, LNZ Vs. enterococci
- **Dalbavancin**
  - Wide range of beta-lactams Vs. MSSA, MRSA, hVISA, VISA
  - No antagonism demonstrated
  - No study to prevent the mergence of resistance

Long-Acting Lipoglycopeptides: Unknowns/Limited Knowledge

Tran TT et al AAC 2022

Efficacy and safety for off-label indications
Optimal dosing for off-label indications
Role and timing in therapy (initial, salvage, consolidation)
Impact on microbiome
Type and accessibility of susceptibility testing techniques
Definition and assessment of tolerance
Combination therapy (*in vivo* or clinical data)
Efficacy against multidrug-resistant pathogens
PK/PD targets
Selection of resistance and mutant selection window
Clinical impact of tolerance, resistance, and cross-resistance
Cost-effectiveness
Safety and tolerability for long-term duration
Appropriate follow-up
Accessibility of susceptibility testing

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

C. difficile Binary Toxin: An Update

Martínez-Meléndez, A. Toxins 2022

- **Infection with *Clostridioides difficile* (CDI)**
  → Mild diarrhea to severe cases of pseudomembranous colitis
- **20% of strains produce a binary toxin (CDT)**
  - Encoded by the tcdA and tcdB genes
  - Possible enhancement of TcdA and TcdB toxicity
- **Role of CDT in CDI remains controversial**
- **A-B-CDT+ *C. difficile* strains**
  - May contain additional antimicrobial resistance determinants
  - Possible contribute to enhanced survival and colonization
  - Minly in hypervirulent strains, especially 027

C. difficile Binary Toxin Producing Strains: Epidemiology

Martínez-Meléndez, A. Toxins 2022

RT	Toxin Genotype	ST	Clade	Characteristics	References
023	$tcdA^+$, $tcdB^+$, $cdtA^+$, $cdtB^+$	5, 22, 25	3	Resistance to erythromycin, levofloxacin, and moxifloxacin. Reports from USA, Northern and Eastern Europe.	[45–47]
027/176	$tcdA^+$, $tcdB^+$, $cdtA^+$, $cdtB^+$	1	2	Strain associated with increased morbidity and mortality. Reports from Korea, Singapore, Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Luxembourg, The Netherlands, Norway, Spain, Sweden, UK, Chile, Panama, Costa Rica, Mexico, Japan, China.	[33,48–55]
033	$tcdA^-$, $tcdB^-$, $cdtA^+$, $cdtB^+$	ND	5	Isolated from a young patient with ulcerative colitis and severe diarrhea in Australia.	[56,57]
078/126	$tcdA^+$, $tcdB^+$, $cdtA^+$, $cdtB^+$	11	5	Community-associated and zoonotic strain with increased morbidity and mortality. Reports from France, Italy, Germany, Taiwan, Czech Republic, Korea, Japan, Australia.	[5,40,41,48,50,57–61]
244	$tcdA^+$, $tcdB^+$, $cdtA^+$, $cdtB^+$	41	2	Community-associated; cause of outbreaks. Reports in Australia, New Zealand.	[44,45,62]
251	$tcdA^+$, $tcdB^+$, $cdtA^+$, $cdtB^+$	231	2	Isolated from three patients in Australia with severe diarrhea, recurrent disease, and one death.	[63]
826	$tcdA^+$, $tcdB^+$, $cdtA^+$, $cdtB^+$	ND	5	Identified in an outbreak in The Netherlands, associated with recurrent and severe disease in two of five patients	[64]
ND	$tcdA^+$, $tcdB^+$, $cdtA^+$, $cdtB^+$	201	3	Isolated from a patient in China, with a severe clinical phenotype; it exhibits a faster germination rate, higher motility, and a higher biofilm formation than RT027 and RT078.	[62,65,66]
ND	$tcdA^-$, $tcdB^-$, $cdtA^+$, $cdtB^+$	11	5	Isolated from a patient in Germany, with eight episodes of CDI ranging from mild to severe symptoms.	[67]

RT: ribotype; ST: Sequence type; ND: no data; CDI: *Clostridioides difficile* infection.

Clinical Infectious Diseases
IDSA GUIDELINES

Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of *Clostridioides difficile* Infection in Adults

Stuart Johnson,[1,2] Valéry Lavergne,[3,4] Andrew M. Skinner,[1,2] Anne J. Gonzales-Luna,[5] Kevin W. Garey,[6] Ciaran P. Kelly,[7] and Mark H. Wilcox[7]

Table 1. Recommendations for the Treatment of *Clostridioides difficile* Infection in Adults

Clinical Presentation	Recommended and Alternative Treatments	Comments
Initial CDI episode	Preferred: Fidaxomicin 200 mg given twice daily for 10 days	Implementation depends upon available resources
	Alternative: Vancomycin 125 mg given 4 times daily by mouth for 10 days	Vancomycin remains an acceptable alternative
	Alternative for nonsevere CDI, if above agents are unavailable: Metronidazole, 500 mg 3 times daily by mouth for 10–14 days	Definition of nonsevere CDI is supported by the following laboratory parameters: White blood cell count of 15 000 cells/μL or lower and a serum creatinine level <1.5 mg/dL
First CDI recurrence	Preferred: Fidaxomicin 200 mg given twice daily for 10 days, OR twice daily for 5 days followed by once every other day for 20 days	…
	Alternative: Vancomycin by mouth in a tapered and pulsed regimen	Tapered/pulsed vancomycin regimen example: 125 mg 4 times daily for 10–14 days, 2 times daily for 7 days, once daily for 7 days, and then every 2 to 3 days for 2 to 8 weeks
	Alternative: Vancomycin 125 mg given 4 times daily by mouth for 10 days	Consider a standard course of vancomycin if metronidazole was used for treatment of the first episode
	Adjunctive treatment: Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics[a]	Data when combined with fidaxomicin are limited. Caution for use in patients with congestive heart failure[b]
Second or subsequent CDI recurrence	Fidaxomicin 200 mg given twice daily for 10 days, OR twice daily for 5 days followed by once every other day for 20 days	…
	Vancomycin by mouth in a tapered and pulsed regimen	…
	Vancomycin 125 mg 4 times daily by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days	…
	Fecal microbiota transplantation	The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation
	Adjunctive treatment: Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics[a]	Data when combined with fidaxomicin are limited. Caution for use in patients with congestive heart failure[a]
Fulminant CDI	Vancomycin 500 mg 4 times daily by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of vancomycin. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal vancomycin, particularly if ileus is present	Definition of fulminant CDI is supported by: Hypotension or shock, ileus, megacolon

Conclusioni

- **Revival dei Gram-positivi**
- **Varietà di classi ed indicazioni**
- **Anche long-life o lineless antibiotics**
  - Dalbavancina & Oritavancina
- **Monoterapia e Combinazione**
  - Fosfomicina Vs. aminoglicosidi
- **Efficacia delle nuove classi in real-life**
- **Grande attività di stewardship**