STEWARDING LONG-ACTING INJECTABLE ANTIMICROBIALS FOR POSITIVE PATIENT IMPACT

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SC Infectious Diseases Society Meeting

Charleston, SC ● January 25, 2025

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DISCLOSURES

- I have no relevant conflicts of interest to report

- Of note, I am a big fan of long-acting injectables…so that may bias my conclusions slightly

OBJECTIVES

- Recall the history and development timeline of long-acting antibacterial injectables
- Discuss the available evidence for dalbavancin and oritavancin in management of invasive infections
- Recommend long-acting lipoglycopeptides (dalbavancin and oritavancin) in both treatment and suppression modalities

AGENDA

- Brief history and profile of the long-acting injectable lipoglycopeptides, dalbavancin and oritavancin
- Overview of the available evidence, with a focus on any RCT data
- Highlight a few potential questions
  - Are these cost effective?
  - How do we steward such costly antibiotics?
  - Are they safe for longterm use?
  - Can they be used for suppression?
  - What is optimal dosing?
  - Is TDM a thing for these antibiotics?

HISTORY OF LONG-ACTING INJECTABLES AND ENTRY INTO INFECTIOUS DISEASES MARKET

- **1966** – first anti-psychotic long-acting injectable (LAI) - fluphenazine enanthate

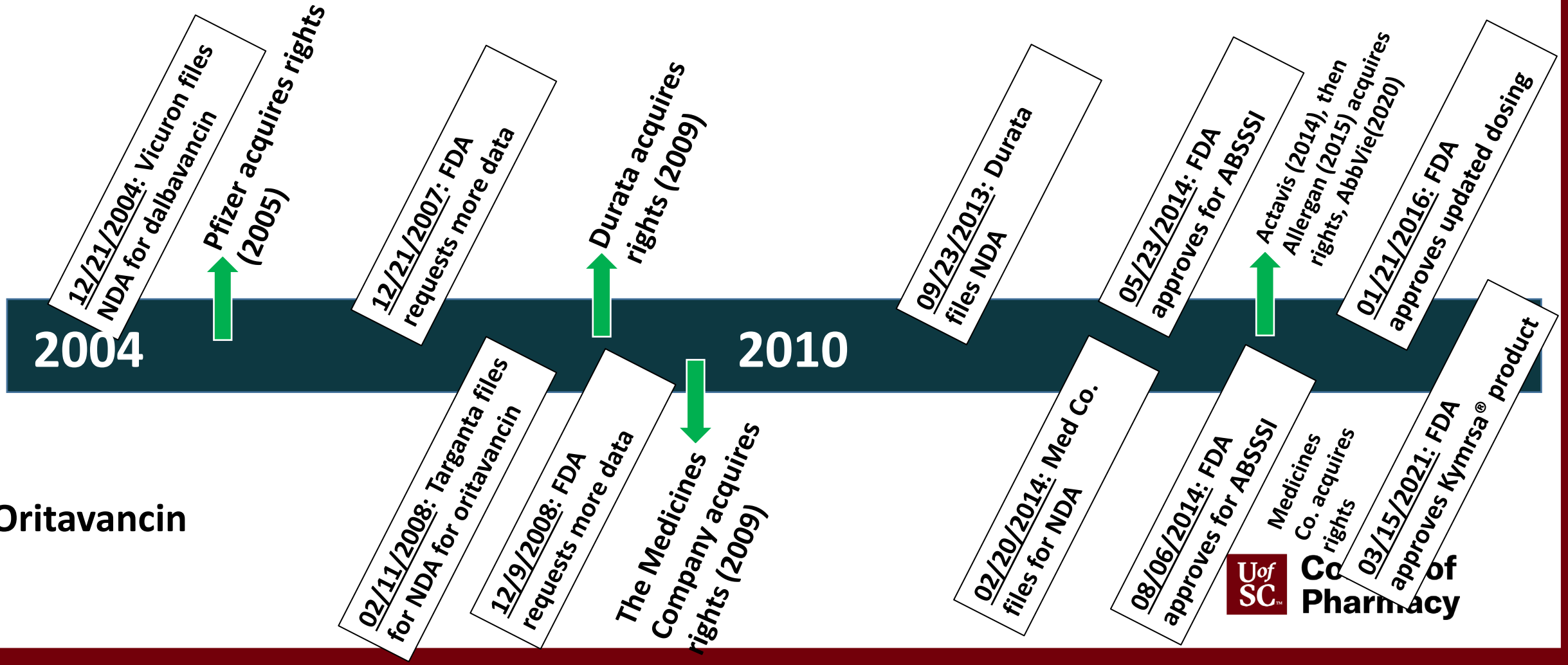
> The concept of antipsychotic LAIs for psychotic illness was not, initially, warmly received by the medical profession (psychiatrists and general practitioners alike). Injectable forms of medication had only previously been used in gynaecology. Also, the case against continuous medication was argued strongly by certain influential psychiatrists and fears of increased side-effects were widespread. Many psychiatrists simply did not accept that an LAI alone would result in an ongoing therapeutic dose, and as a consequence wanted to add oral medication as an 'insurance strategy'. Even more importantly, the increasingly vocal groups interested in

Johnson DAW. *British Journal of Psychiatry*. 2009;195(S52):s7-s12. doi:10.1192/bjp.195.52.s7

Dalbavancin & Oritavancin History

Available at:
https://www.drugs.com/history/orbactiv.html
https://www.drugs.com/history/dalvance.html

Dalbavancin



Oritavancin

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Comparing Properties of Dalbavancin and Oritavancin

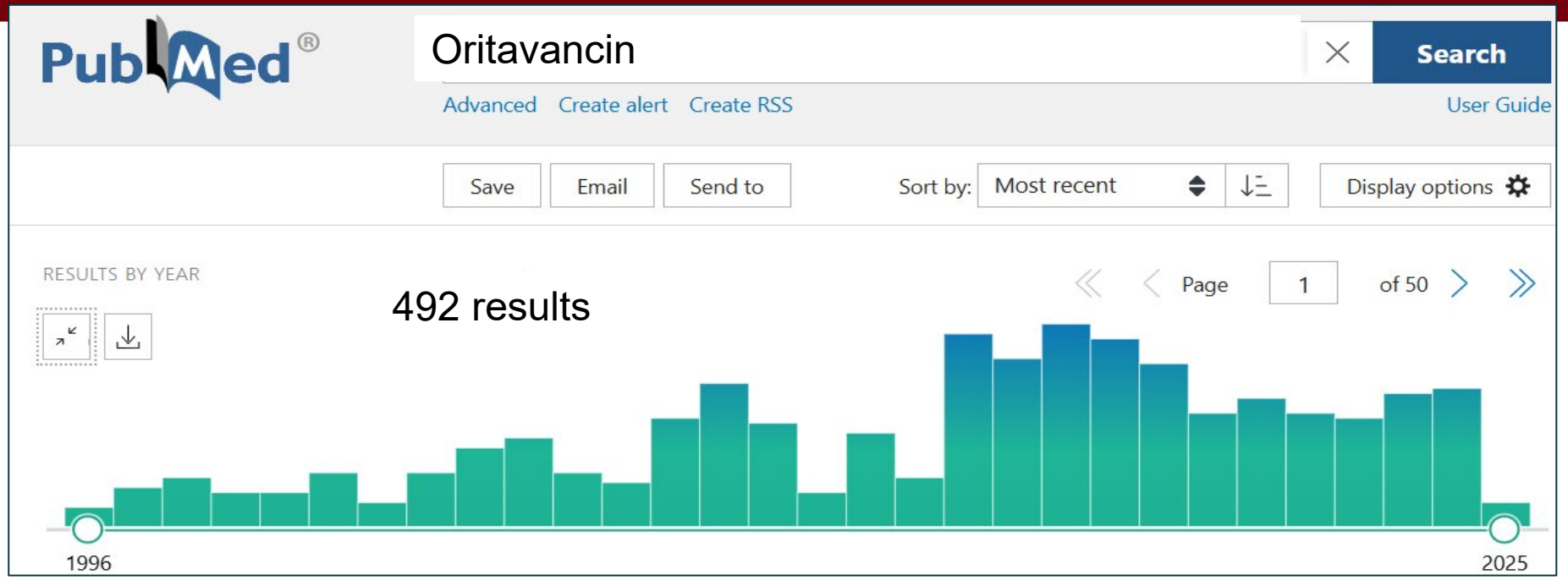
Characteristic	Dalbavancin	Oritavancin[1]
Indications (FDA approved)	ABSSSI	ABSSSI
Dosing (FDA approved)	Single dose 1500mg or 1gram x 1, followed by 500mg q1week	Single dose 1,200mg
Infusion time	30 minutes	1 hour (original formulation = 3 hours)
Half-life	150-250 hours	~400 hours
ADE	Mild, mostly GI	Mild, mostly GI, infusion-related reaction
Renal dose adjustment	Requires dose adjustment at CrCL <30ml/min	No dose adjustment required
Drug-drug/lab interactions	None known to be clinically relevant	Weak 3A4/2D6 inducer; weak 2C9/C19 inhibitor May interfere with coagulation testing
Spectrum of activity	Gram-positive organisms	Gram-positive organisms including VRE (van-A & van-B)

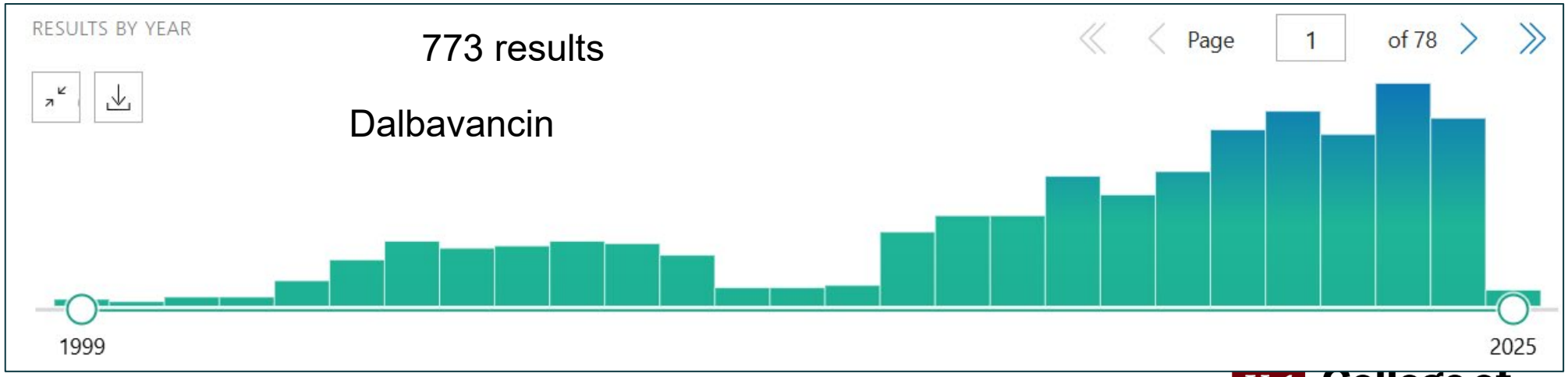
FDAaccess.gov

Zhanel GG, et al. Drugs 2010;70:859-86.

[1]New formulation contains cyclodextrin (< 3g)

Pubmed.gov





SCHOLARSHIP ON THE RISE

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DALBAVANCIN FOR INVASIVE AND COMPLICATED GRAM-POSITIVE INFECTIONS – WHAT'S THE EVIDENCE?

Reference	*n*	NV/PV/CD or IAI/BJI	Bacterium or bacteria (*n*)[b,c]	Most frequent dosing	Duration/no. of doses	Success, *n* (%)[d]	Adverse events (*n*)
Infective endocarditis		NV/PV/CD					
Tobudic et al., 2018 (84)	27	15/7/5	*S. aureus* (9), CoNS (7), *E. faecalis* (4), other (9)	1,500 mg LD then 1,000 mg every 2 wk or 1,000 mg LD then 500 mg weekly	Median, 6 wk (range, 1–30)	25 (93)	Nausea (1), RCI (1)
Bouza et al., 2018 (85)	7	Not specified[e]	*S. aureus* (1), CoNS (2), *Enterococcus* spp. (2), other (2)[f]	1,000 mg LD then 500 mg weekly	Median, 3 doses (range, 1–24)	6 (86)	Rash (2), tachycardia (2), RCI (2), nausea (1), rectal bleeding (1)[g]
Hidalgo-Tenorio et al., 2019 (86)	34	11/15/8	*S. aureus* (10), CoNS (15), *E. faecalis* (3), other (7)	1,000 mg once or 1,500 mg LD then 500 mg at day 8	Median, 14 days (IQR, 14–21)	33 (97)	Fever (1), renal failure (1)
Bryson-Cahn et al., 2019 (87)	9	9/–/–	*S. aureus* (9)	1,000 mg once or 1,000–1,500 mg LD then 500 mg day 7	2 doses	9 (100)	Not reported
Wunsch et al., 2019 (88)	25	15/6/4	Not specified[e]	1,000 mg LD then 500 mg weekly or 1,500 mg once or 1,500 mg weekly × 2[g]	Median, 3 doses (range, 1–32)[g]	23 (92)	Dyspnea (1), hypertension during infusion (1), fatigue and vertigo (1)[g]
Dinh et al., 2019 (89)	19	9/10/–	Not specified[e]	1,500 mg once or 1,500 mg LD then 1,000–1,500 mg at day 7 or 14	1–2 doses	13 (68)	Hypersensitivity (2), headache (1), eosinophilia (1), phlebitis (1)[g]
Bork et al., 2019 (111)	7	Not specified[h]	Not specified[e]	Not specified[e]	Median, 4 doses	4 (57)	Acute kidney injury (2), rash and pruritus (1)[g]
Veve et al., 2020 (112)	12	Not specified[e]	Not specified[e]	1,500 mg once, 1,500 mg for 2 doses at day 1 and day 7, or 1,500 mg for 2 doses at day 1 and day 14	1–2 doses	NA (91)[i]	Catheter infection (1), hypersensitivity (1)[g]
Total	140	59[j]/38/18				113[j] (88)	

Tran T, et al. AAC 2022

DALBAVANCIN FOR INVASIVE AND COMPLICATED GRAM-POSITIVE INFECTIONS – WHAT'S THE EVIDENCE?

Bone and joint infections		IAI/BJI					
Rappo et al., 2019 (93)	67	–/67	*S. aureus* (42), CoNS (14), *Enterococcus* (8), other (33)[f]	1,500 mg weekly × 2	2 doses	65 (97)	Drug-related treatment adverse event (1)
Bouza et al., 2018 (85)	33	20/13	*S. aureus* (9), CoNS (16), *Enterococcus* spp. (3), other (6)[f]	1,000-mg LD then 500 mg weekly	Median, 3 doses (range, 1–24)[g]	28 (85)	Rash (2), tachycardia (2), RCI (2), nausea (1), rectal bleeding (1), candidiasis (1)[g]
Morata et al., 2019 (95)	64	45/19	*S. aureus* (14), CoNS (33), *Enterococcus* spp. (9), other (22)[f]	1,000-mg LD then 500 mg weekly	Median, 5 doses	45 (70)	GI problems (3), rash (1), phlebitis (1), asthenia (1), RCI (1)
Almangour et al., 2019 (96)	31	–/31	*S. aureus* (27), CoNS (1), other (6)[f]	1,000 mg LD then 500 mg weekly or 1,500 mg weekly × 2	Median, 3 doses	28 (90)	None
Tobudic et al., 2019 (97)	46	8/38	Not specified[k]	1,500 mg LD then 1,000 mg every 2 wk, 1,000 mg LD then 500 mg weekly, or 1,500 mg LD then 1,500 mg at day 8[g]	Range, 2–32 doses[l]	30 (65)	Nausea (1), exanthema (2), hyperglycemia (1)[g]
Dinh et al., 2019 (89)	48	–/48	Not specified[k]	1,500 mg every 7–14 days × 2 or 1,500 mg once	Range, 1–10 doses	35 (73)	Hypersensitivity (2), headache (1), eosinophilia (1), phlebitis (1)[g]
Wunsch et al., 2019 (88)	62	32/30	Not specified[k]	1,000 mg LD then 500 mg weekly, 1,500 mg once, or 1,500 mg weekly × 2[g]	Median, 3 doses (range, 1–32)[g]	58 (94)	Dyspnea (1), hypertension (1), fatigue and vertigo (1)[g]
Matt et al., 2021 (98)	17	17/–	*S. aureus* (10), CoNS (10), *E. faecalis* (1), other (5)[f]	1,500 mg weekly × 2 or 1,500 mg once	Median, 2 doses (range, 1–10)[g]	8 (47)	None
Buzón-Martín et al., 2019 (99)	16	16/–	*S. aureus* (6), CoNS (7), *Enterococcus* spp. (6)	1,500 mg LD, then 500 mg on day 7, then 500 mg every 2 wk	Range, 6–12 wk	11 (69)	Leukopenia (1), rash (1)
Bork et al., 2019 (111)	15	Not specified	Not specified[e]	Not specified[e]	Median, 4 doses	7 (47)	Acute kidney injury (2), rash and pruritus (1)[g]
Veve et al., 2020 (112)	49	Not specified	Not specified[k]	1,500 mg once, 1,500 mg for 2 doses at day 1 and day 7, or 1,500 mg for 2 doses at day 1 and day 14	1–2 doses	NA (91)[i]	Catheter infection (1), hypersensitivity (1)[g]
Cojutti et al., 2021 (94)	15	11/4	*S. aureus* (5), CoNS (9), *E. faecalis* (1)	1,500 mg weekly × 2	2 doses	12 (80)	None
Total	463	149/250[j]				327[j] (79)	

Tran T, et al. AAC 2022

OUTCOMES BY SYNDROME & ORGANISM

- Bone and joint infections
  - 12 studies, n=463 patients, prosthesis associated (n=149)
  - *S. aureus* (n=113), CoNS (n=90), Enterococcus spp. (n=28)
  - **Success: 79%**

- IE
  - 8 studies, n=140 patients, native valve (n=59), prosthetic valve (n=38), cardiac device (n=18)
  - *S. aureus* (n=29), CoNS (n=24*), Enterococcus spp.* (n=9), others
  - **Success: 88% (113/140)**

Tran T, et al. AAC 2022

ON THE FLIP SIDE…ORITAVANCIN EVIDENCE FOR INVASIVE AND COMPLICATED GRAM-POSITIVE INFECTIONS

Reference	*n*	Infection(s)	Bacterium or bacteria (*n*)	Most frequent dosage(s)	Duration/ no. of doses	Success, *n* (%)[b]	Adverse event(s) (*n*)
Bloodstream infections							
Bhavnani et al., 2006 (73)	55	Bacteremia	*S. aureus* (55)	5–10 mg/kg/day	10–14 days	45 (78)	N/R
Johnson et al., 2015 (109)	1	PVE	VR *E. faecium* (1)	1,200 mg every 48 h × 3 doses, then 1,200 mg weekly × 6 wk, then 1,200 mg biweekly × 10 wk	14 doses	1 (100)[c]	Anorexia, nausea, elevated LFTs (1)
Stewart et al., 2017 (82)	6	Bacteremia[d]	MSSA (4), CoNS (1), *Enterococcus* spp. (1)	1,200 mg	1 dose	4 (66.7)	None
Stewart et al., 2017 (82)	1	NVE	*S. agalactiae* (1)	1,200 mg	1 dose	0 (0)	None
Datta et al., 2018 (74)	3	Bacteremia	MRSA (1), *S. gallolyticus* (1), *Granulicatella adiacens* (1)	1,200 mg	1 dose	3 (100)	N/R
Brownell et al., 2020 (76)	4	Endocarditis	Not specified[e]	1,200 mg then 800–1,200 mg weekly	N/R[e]	4 (100)	None
Redell et al., 2019 (77)	7	Bacteremia	MRSA (2), MSSA (1), *S. epidermidis* (2), other (2)	1,200 mg once	1 dose	7 (100)	Not specified (29)[f]
Schulz et al., 2018 (80)	1	Bacteremia	VR *E. faecium* (1)	1,200 mg then 800 mg weekly	4 doses	0 (0)	None
Total	78					64 (82)	
Bone and joint infections							
Van Hise et al., 2020 (75)	134	Acute osteomyelitis	MSSA (35), MRSA (108), VISA (2), VRE (7)	1,200 mg once then 800 mg weekly	4–5 doses	118 (88.1)	Hypoglycemia (3), tachycardia (2)
Brownell et al., 2020 (76)	16	Osteomyelitis, diabetic foot, IAI	Not specified[g]	1,200 mg then 800–1,200 mg weekly	N/R[g]	16 (100)	Not specified (3)[f]
Redell et al., 2019 (77)	25	Acute osteomyelitis, septic arthritis, IAI	Not specified[g]	1,200 mg once or 1,200 mg every 6–14 days	1–10 doses	19 (76)	Not specified (29)[f]
Chastain and Davis, 2019 (78)	9	Chronic osteomyelitis	MRSA (5), other (4)[i]	1,200 mg LD then 1,200 mg every 13–52 days	2–6 doses	9 (100)	None
Dahesh et al., 2019 (66)	1	IAI	VR *E. faecium* (1)	1,200 mg weekly × 2 wk then 800 mg weekly	10 doses	1 (100)	N/R
Ruggero et al., 2018 (79)	1	Acute osteomyelitis	MRSA (1)	1,200 mg every 2–4 wk	5 doses	1 (100)	N/R
Schulz et al., 2018 (80)	4	Acute and chronic osteomyelitis, septic arthritis, diskitis	MSSA (1), other (3)[i]	1,200 mg then 800 mg weekly	2–8 doses	2 (50)[h]	Anemia and leukopenia (1)
Foster et al., 2017 (110)	1	IAI	Daptomycin-nonsusceptible VR *E. faecium* (1)	1,200 mg weekly	6 doses	1 (100)	None
Delaportas et al., 2017 (81)	1	Acute osteomyelitis	MSSA (1)	1,200 mg weekly	7 doses	1 (100)	None
Stewart et al., 2017 (82)	1	Bursitis	MRSA (1)	1,200 mg once	1 dose	1 (100)	Hearing loss (1)
Total	193					169 (87.6)	

- Several retrospective or observational cohorts ranging in type of invasive infection
- A bit more limited in number of patients than dalbavancin evidence
- Overall, results are positive without a signal really for a particular risk of failure

CAN I POSITION THESE FOR SUPPRESSION? (EXAMPLE DALBAVANCIN)

METHODS

Study Design: Multicenter, retrospective cohort study	Setting: Multicenter, Data analyzed at Prisma Health Richland	Study Time Period: January 1, 2018 – April 9, 2023
Statistical analyses: Safety & effectiveness analysis; frequency of dosing profiled	Inclusion: • ≥ 18 years of age • ≥ 1 dose of dalbavancin administered for suppression therapy	Exclusion: • Only received dalbavancin for treatment of an active infection

Most Common Dosing Regimens
• 1000 mg IV every 4 weeks • 1500 mg IV every 2 weeks • 1000 mg IV every 2 weeks
Duration of Suppression Therapy, months
• Mean (SD): 6.5 (4.6)
Proportion of Patients Experiencing Hospitalization or Microbiological Recurrence Due to Index Organism
• 8 of 40 patients (20%)
Time to Event, months

• Hospitalization, mean (SD)
  • 6.9 (3.7)
• Microbiological recurrence, mean (SD)
  • 7.6 (3.2)

Characteristic	Total n=40
Indication for suppression therapy (n = 40)	
• LVAD[1] driveline infection, n (%)	22 (55)
• Prosthetic joint infection, n (%)	8 (20)
• Osteomyelitis with retained hardware, n (%)	5 (12.5)
• Other/unknown, n (%)	5 (12.5)

- Suppression in this cohort was effective and safe
- Ensuring continuous therapy is valuable
- Role for TDM to guide long-term therapy?

Shaw M, Derrick C, et al. Presented at IDWeek2023

DO WE HAVE ANY PUBLISHED RCT DATA OUTSIDE OF ABSSSI?

Rappo, et al (Osteomyelitis – Phase 2)

Objective:

- Assess efficacy and safety of dalbavancin as a 2-dose regimen for osteomyelitis

Methods:

- Randomized, open-label, comparator-controlled trial (phase II trial)
  - March 2016 – December 2017
  - Cherkasy, Ukraine (860 bed tertiary care teaching hospital) → site previously participated in 3 dalbavancin trials
- Inclusion: Adults with first episode of osteomyelitis
- Exclusion: > 24 h of IV antibiotics within 96 hours of randomization, ***complicating factors***
- Distribution 7:1 to dalbavancin (1500 mg on days 1 and 8) vs standard of care (SOC) for osteomyelitis (per investigator judgement, 4-6 weeks duration, oral or IV)

Rappo U, et al. Open Forum Infectious Diseases. 2019: ofy331.

RAPPO, ET AL (OSTEOMYELITIS – PHASE 2)

Results:

- Dalbavancin (n = 70), SOC (n = 10)
- All had baseline debridement
- Staphylococcus aureus was most common pathogen
  - 60% of patients
- Clinical cure at day 42:
  - Dalbavancin: 97%
  - SOC: 88%
- Clinical response similar at day 21, 6 mo and 1 year

SOC Regimens:
- Vancomycin IV
- Vancomycin IV → linezolid

Dalbavancin arm:
- 3 patients did not receive 2nd dose

Rappo U, et al. Open Forum Infectious Diseases. 2019: ofy331.

RCTS IN PROGRESS FOR INVASIVE INFECTIONS: DALBAVANCIN OR ORITAVANCIN

NCT05117398 (France)

Recruiting

Dalbavancin Versus Standard Antibiotic Therapy for Catheter-related Bloodstream Infections Due to Staphylococcus Aureus

NCT00057369 (Georgia, USA)

Unknown status *

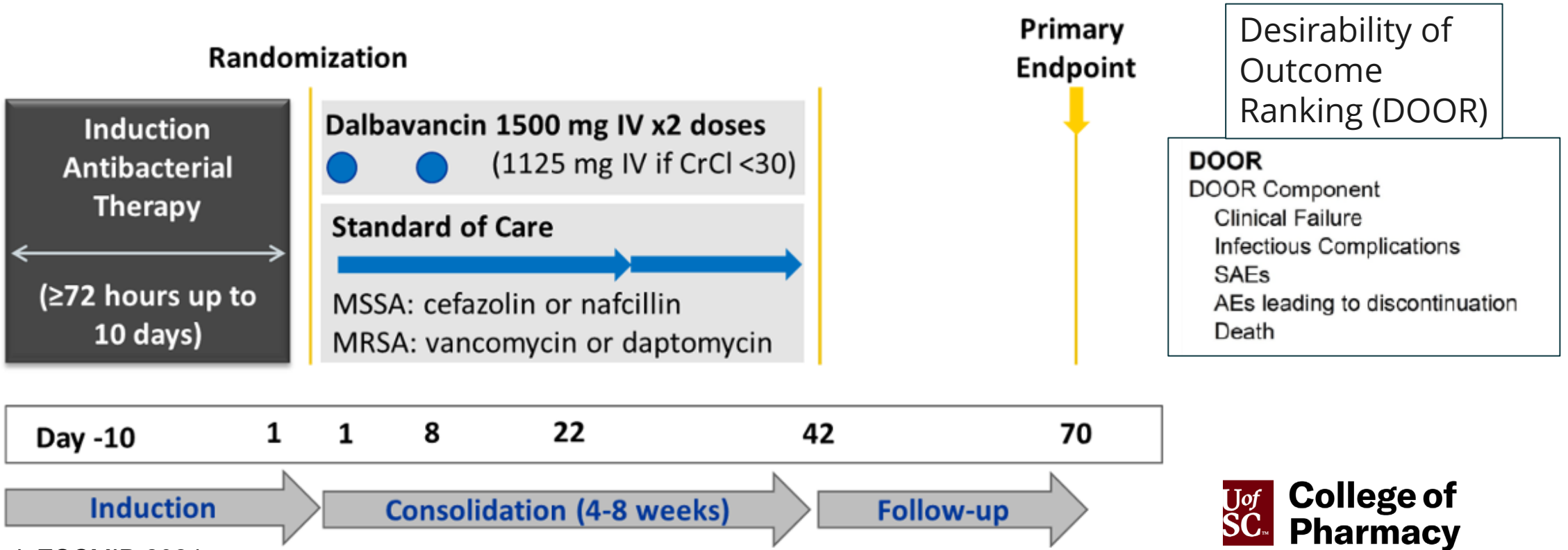
Safety and Efficacy of Dalbavancin Versus Vancomycin in the Treatment of Catheter-Related Bloodstream Infections

- Raad I, et al. conducted and published a previous small Phase 2 trial for CLABSI showing effectiveness compared to SOC

Available at: https://clinicaltrials.gov/

DO WE HAVE ANY PUBLISHED RCT DATA OUTSIDE OF ABSSSI? --- DOTS STUDY

- Complicated bacteremia (w/ or w/o right-sided IE) who had sterile blood cultures randomized to dalbavancin vs. SOC



Turner et al. ESCMID 2024

PATIENT BASELINE VARIABLES

Characteristic	Dalbavancin (n=100)	SOC (n=100)
Age, median (SD), years	54.3 (15.7)	54 (16.8)
Sex, male	70	68
Race/Ethnicity		
White	68	69
Black	20	29
Asian	5	1
Indigenous	2	0
Hispanic/Latino	11	14
Unknown	5	1
PWID	16	13
Comorbidity		
Heart failure	21	19
Chronic kidney disease	20	30
Diabetes mellitus	44	48
Liver disease	14	8
Cancer	21	17
Immune suppression	35	26
Pathogen		
MRSA	34	32
MSSA	66	68
Infection Characteristic[a], %		
Osteoarticular	28.9	34
Skin	33.9	29.2
Endovascular	19.8	24.5
Pulmonary	17.4	13.2

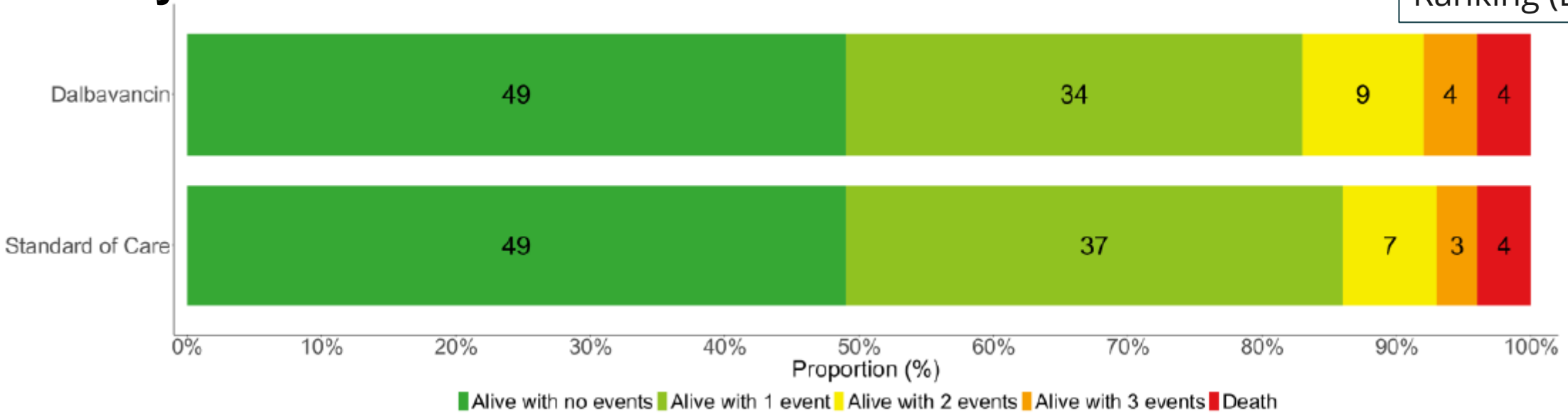
Turner et al. ESCMID 2024

Safety Outcomes

AEs	Dalbavancin (n=100)	SOC (n=100)
SAEs	43	37
Related SAEs	2	4
AEs leading to discontinuation	3	12

Efficacy Outcomes

Desirability of Outcome Ranking (DOOR)



Non-inferiority of dalbavancin (n=100) to SOC (n=100) was demonstrated by clinical efficacy (95% CI); **73% (64-82) and 72% (63-81)**, respectively (difference, 95% CI: 1% (-12 to 14%).

Turner et al. ESCMID 2024

EXAMINING STUDIES WITH MATCHED COHORTS FOR RELEVANT NON-CLINICAL OUTCOMES

- **Antosz et al.**
  - Matched cohort (1:1) Dalbavancin or oritavancin (n=23) to SOC (n=23)
  - Bacteremia (35%), IE (39%), Osteomyelitis (22%)
  - Key results:
    - Composite clinical success at 90 days similar (79% vs. 70%)
    - **26% left AMA in SOC arm** prior to completing therapy (0% in dalba)
    - **Clinic follow-up 30% in dalbavancin** group vs. 13% in SOC

- **Cain et al.**
  - Osteomyelitis
  - Matched cohort (1:2) Dalbavancin (n=42) to SOC (n=90)
  - Key results:
    - Treatment success at 1 year similar (79% vs. 77%)
    - **17.8% of patients in SOC had PICC-line complications**

Antosz K, et al. 2021 Pharmacy
Cain A, et al. 2022 OFID

SAFETY CONCERNS?

- Adverse events documented are typically mild (e.g. GI, headache, non-severe rash) and infrequent in occurrence
  - ~3-11% in most published reports
  - One comparator cohort suggested > ADEs with oritavancin compared to dalbavancin (non-controlled, retrospective in nature)

- Limited number of serious ADEs noted in cohort studies and clinical experience
  - Long-term use (up to 6-9 months) with rare discontinuations due to ADEs

Tran T, et al. AAC 2022
Crocker J, et al. IDWeek 2024
Shaw M, et al. IDWeek 2023

CROSS REACTIVITY CONCERN IN VANCOMYCIN ALLERGIC PATIENTS?

- Lack of cross reactivity demonstrated in patients with history of vancomycin-associated DRESS
  - *HLA-A∗32:01*–positive individuals
- Favorable tolerance of dalbavancin among patients with documented vancomycin intolerance in the EHR
- No data suggesting issues with oritavancin in vancomycin intolerance

Nakkam N, et al. J Aller Clin Immunol 2020
Freeman K, et al. OFID Nov 2021 (Abstract)

ORITAVANCIN PROFILE

- SOLO I/II study of oritavancin versus vancomycin for ABSSSI
- 6 cases of osteomyelitis reported in the oritavancin treated patients compared to 1 case in the vancomycin arm
  - Median time to osteomyelitis was 4.6 days (0-9)
- Warning in manufacturer's labeling
  - *Does this concern you as a prescriber?*

----------WARNINGS AND PRECAUTIONS----------

- Coagulation test interference: Oritavancin has been shown to artificially prolong aPTT for up to 120 hours, and may prolong PT and INR for up to 12 hours and ACT for up to 24 hours. For patients who require aPTT monitoring within 120 hours of KIMYRSA dosing, consider a non-phospholipid dependent coagulation test such as a Factor Xa (chromogenic) assay or an alternative anticoagulant not requiring aPTT. (5.1, 7.2)
- Serious hypersensitivity reactions, including anaphylaxis, have been reported with the use of oritavancin products, including KIMYRSA. Discontinue infusion if signs of acute hypersensitivity occur. Carefully monitor patients with known hypersensitivity to glycopeptides. (5.2)
- Infusion Related Reactions: Infusion related reactions have been reported with the glycopeptide class of antimicrobial agents, including oritavancin products (e.g. KIMYRSA). Stopping or slowing the infusion may result in cessation of these reactions. (5.3)
- *Clostridioides difficile*-associated diarrhea: Evaluate patients if diarrhea occurs. (5.4)
- Concomitant warfarin use: Oritavancin has been shown to artificially prolong PT/INR for up to 12 hours (5.1). Patients should be monitored for bleeding if concomitantly receiving KIMYRSA and warfarin. (5.5)
- Osteomyelitis: Institute appropriate alternate antibacterial therapy in patients with confirmed or suspected osteomyelitis. (5.6)

FDAaccess.gov

Corey RG, et al. Antimicrob Agents Chemother 2018

THE DANGER AHEAD? ACQUIRED RESISTANCE ON THERAPY: A SMATTERING OF CASES

- Werth B, et al: MRSA central line-associated bloodstream infection treated with vancomycin x12d, then dalbavancin in HD patient (single 1g dose)
  - BSI resolved, but urine MRSA with VISA and dalba-R
- Steele JM, et al: MRSA tricuspid IE in a pregnant patient treated sequentially with vancomycin and dalbavancin
  - Breakthrough bacteremia with VISA, telavancin non-susceptible at week 4
- Zhang R, et al: ESRD patient with MRSA AVF infection received x 2 doses dalba
  - Developed IE (by TEE) at 5 wks, with vanc, dapto, dalba non-susceptible isolate; walK, scrA
- Additional cases captured among treatment failures in the larger cohorts

Werth BI, et al. Clin Microbiol Infect 2018;24:429-3.
Steele JM, et al. J Clin Pharm Ther 2018;43:101-3.
Zhang R, et al. CID 2022; ciac341.

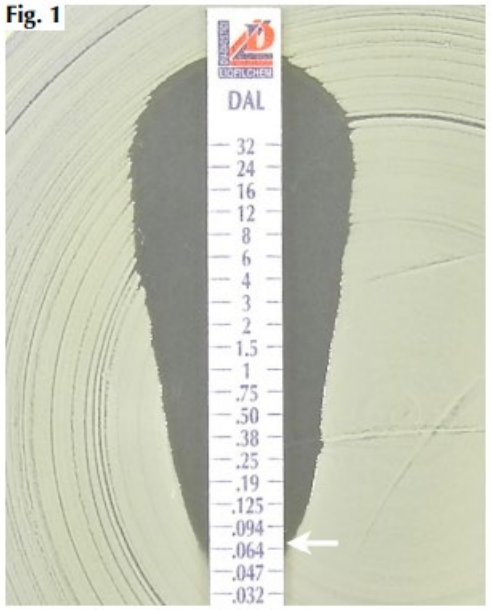
OVERLAPPING RESISTANCE MECHANISMS

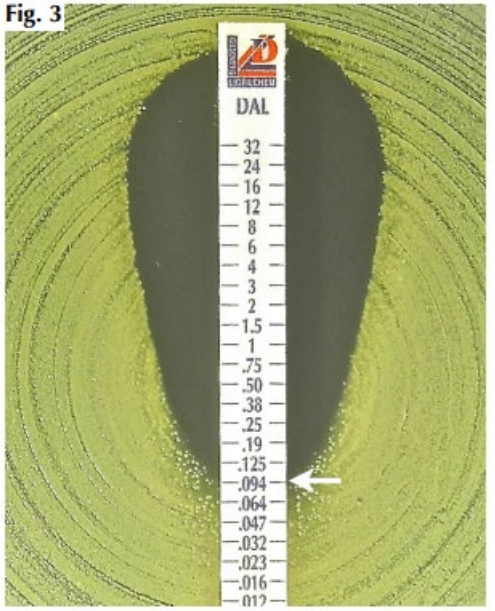
- Oritavancin: van gene cluster mediated, horizontal gene transfer
  - Generally active against vanA or vanB mutations, but multiple copies can confer resistance in VRE. vanS, vanZ can also trigger VRE resistance.
  - vanZ applies to *Strep, Enterococcus, C. difficle, Bacillus spp., S. aureus*, and can transfer from *Enterococcus to S. aureus*.
- Dalbavancin: similar to teicoplanin and vanc but can also have VISA phenotype via walKR and vraTSR, as well as via cell wall/membrane changes.
  - May influence daptomycin cross sensitivity

Hines KM, et al. 2020. J Antimicrob Chemother 75:1182–1186.
Werth BI, et al. Clin Microbiol Infect 2018;24:429-3.
Zhang R, et al. CID 2022; ciac341.
Tran TT, et al. Antimicrobial Agents Chemotherapy 2022..

MIC TESTING - DALBAVANCIN

- Liofilchem test strips are approved and available for dalbavancin
- Can’t we just use vancomycin as a surrogate?





Information available at: https://www.liofilchem.net/login.area.mic/technical_sheets/MTS38.pdf

SUSCEPTIBILITY TESTING – ORITAVANCIN

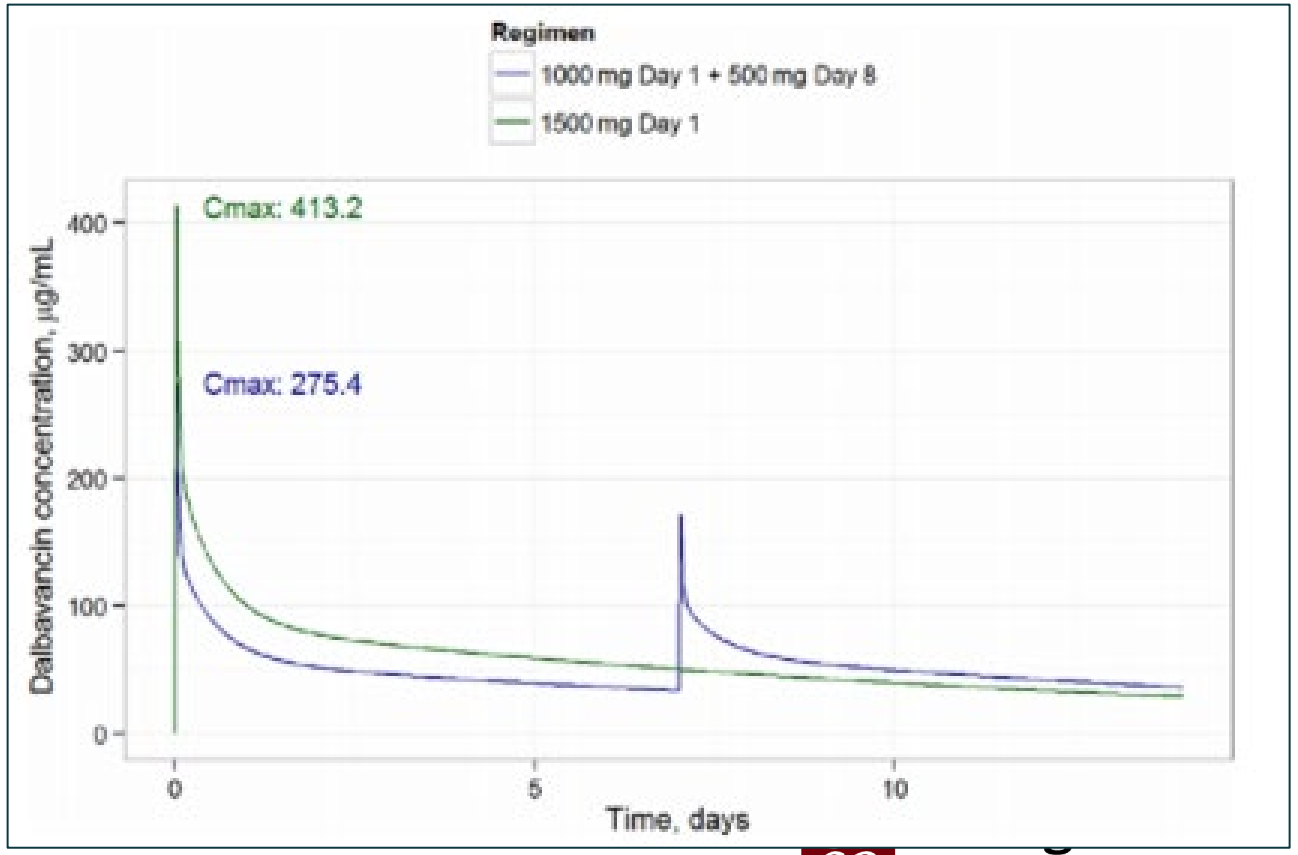
- Three options
  - Reference lab
  - Standard microdilution broth plates
    - Polysorbate-80 required
  - Custom plates
- ARUP will return results in 2-4 days
  - Interpretation available for *S. aureus*, *E. faecalis* and *E. faecium*

ATCC reference strain (medium)	MIC (µg/mL) for Antibacterial agents with (+) and without (-) Polysorbate-80 (P80)[a]							
	Oritavancin		Vancomycin		Teicoplanin		Ciprofloxacin	
	-P80	+P80	- P80	+P80	-P80	+P80	-P80	+P80
S. aureus ATCC 29213 (CAMHB)	1	0.03	1	1	0.5	0.5	0.5	0.5
S. aureus ATCC 29213 (CAMHB+ 2% LHB)	0.03	0.03	1	1	1	0.5	0.5	0.5
E. faecalis ATCC 29212 (CAMHB)	0.5	0.03	4	4	0.5	0.5	0.5	0.5
E. faecalis ATCC 29212 (CAMHB+ 2% LHB)	0.016	0.03	2	4	1	0.5	0.5	0.5
S. pneumoniae ATCC 49619 (CAMHB+ 2% LHB)	0.001	0.002	0.25	0.25	0.03	0.03	0.5	1
S. pneumoniae ATCC 49619 (BHI)	0.008	0.001	0.25	0.25	0.03	0.03	0.5	0.5
S. pneumoniae ATCC 49619 (BHI+ 2%LHB)	0.001	0.001	0.25	0.25	0.03	0.03	0.5	1

Available at: https://melintamedicalaffairs.com/IDWeek2023/PDFs/ORB-LAB-SRD%20Antimicrobial%20Susceptibility%20Testing_FINAL_09Aug23.pdf?apdf=2

Dalbavancin Pharmacokinetic & Pharmacodynamic Dive

- 3-compartment distribution model w/ first-order elimination
- Vd ~ 15L; 93% protein bound
- Only factors majorly impact PK is severe renal impairment
- >99% target attainment up to MIC of 2mcg/mL with standard regimens approved for ABSSSI



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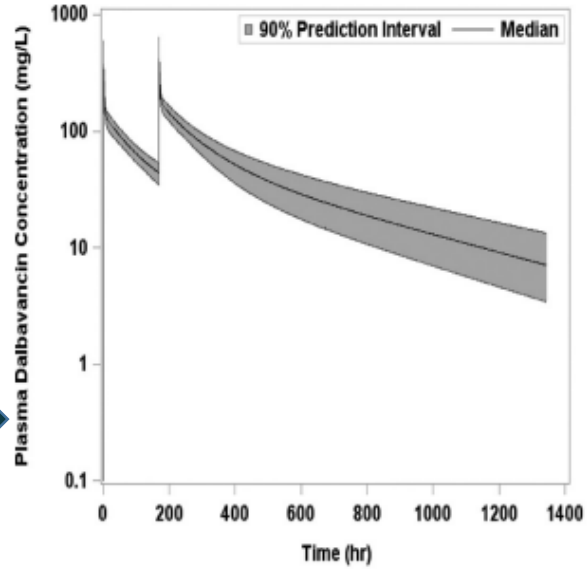
Accessdata.fda.gov

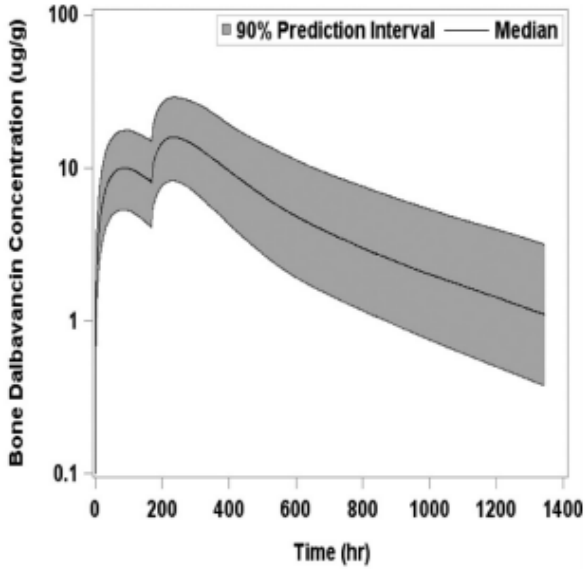
Carrothers TJ, et al. Clin Pharmacol Drug Dev 2020;9:21-31.

Dalbavancin PK in plasma & bone

- Cortical bone concentrations=6.3 mcg/g (12 hours) and 4.1 mcg/g 2 weeks post-dose

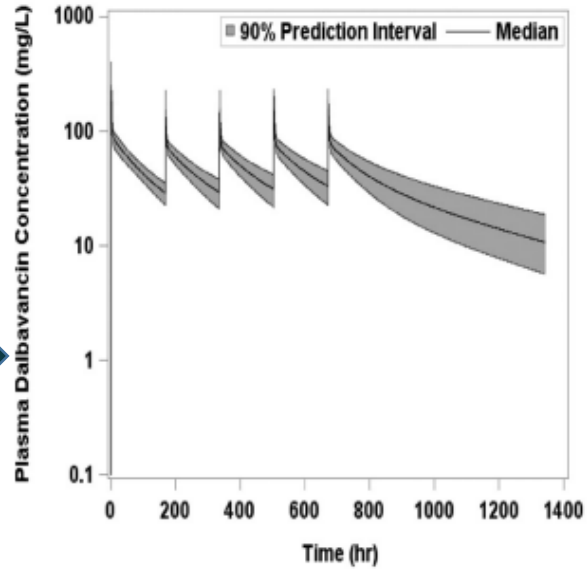
1,500 mg x 2 doses, q1 week

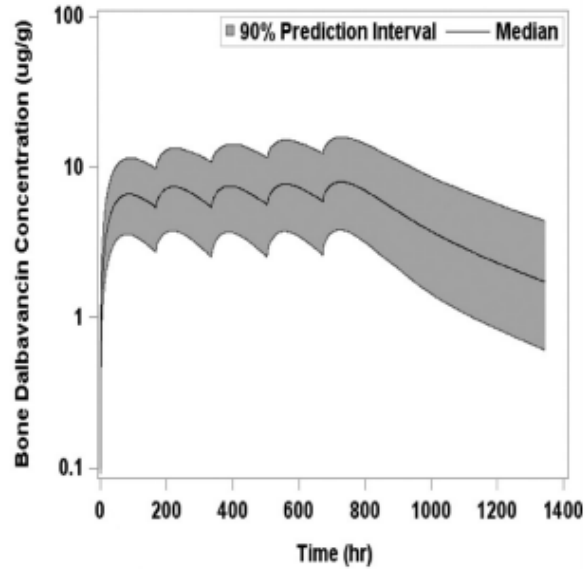




- 1,500 mg doses given on days 1 and 8 exceeds MIC_{90} for *S. aureus* for up to 8 weeks in both bone and plasma

1,000 mg x 1, 500mg q weekly x 5





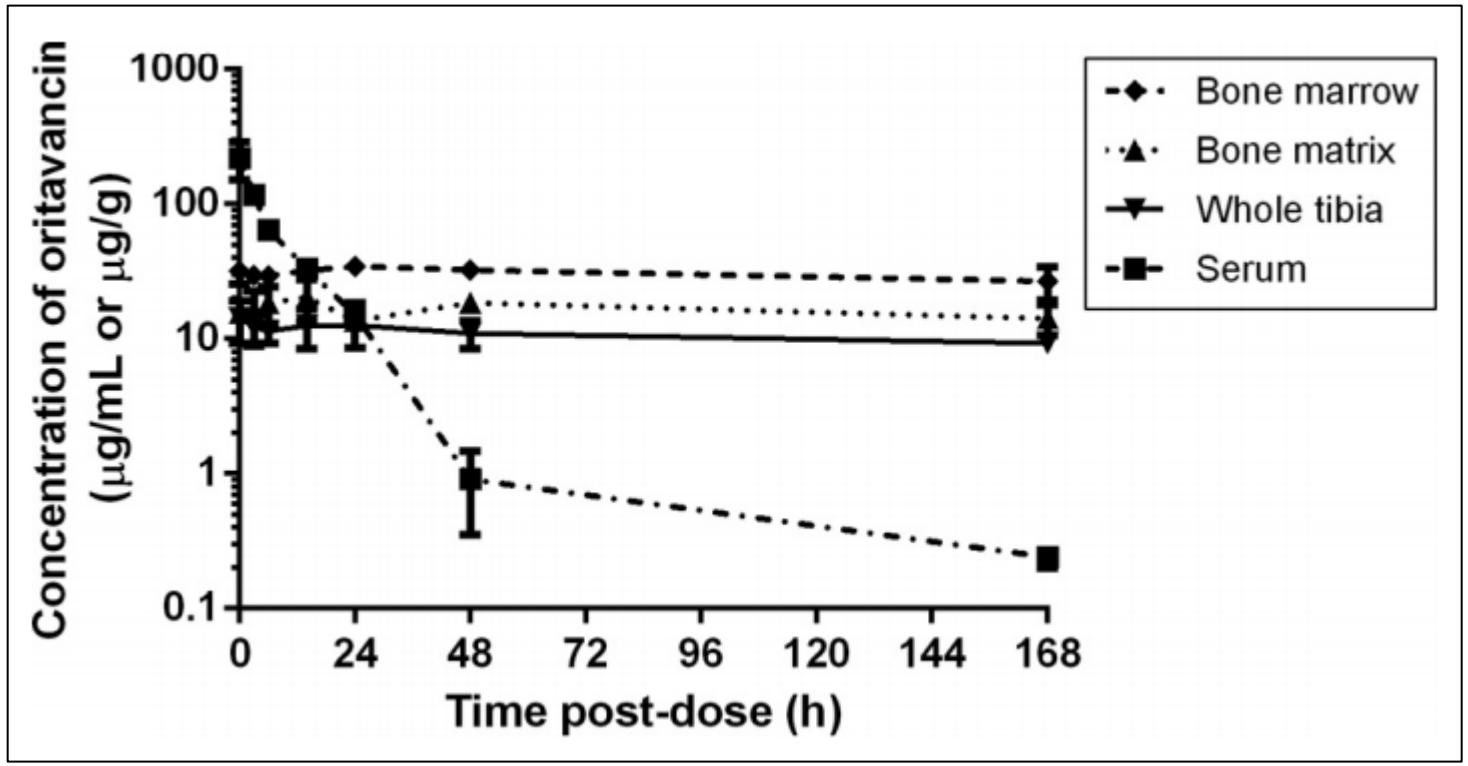
Dunne MW, et al. Antimicrob Agents Chemother 2015;59:1849-5.

Take home on consolidated, multi-dose dalbavancin

1500mg dose on day 1, followed by 1500 mg on day 8 gives sustained concentrations in bone & serum above MIC_{90} for at least ~6-8 weeks

Oritavancin Pharmacokinetic & Pharmacodynamic Dive

- Vd = 70-80 L
- Protein binding: 85-90%
- Rabbit model 20mg/kg single dose (equivalent 1200mg)
- Bone (AUC_{0-168}) tissue:serum ratio bone matrix 1.7, bone marrow 3.1

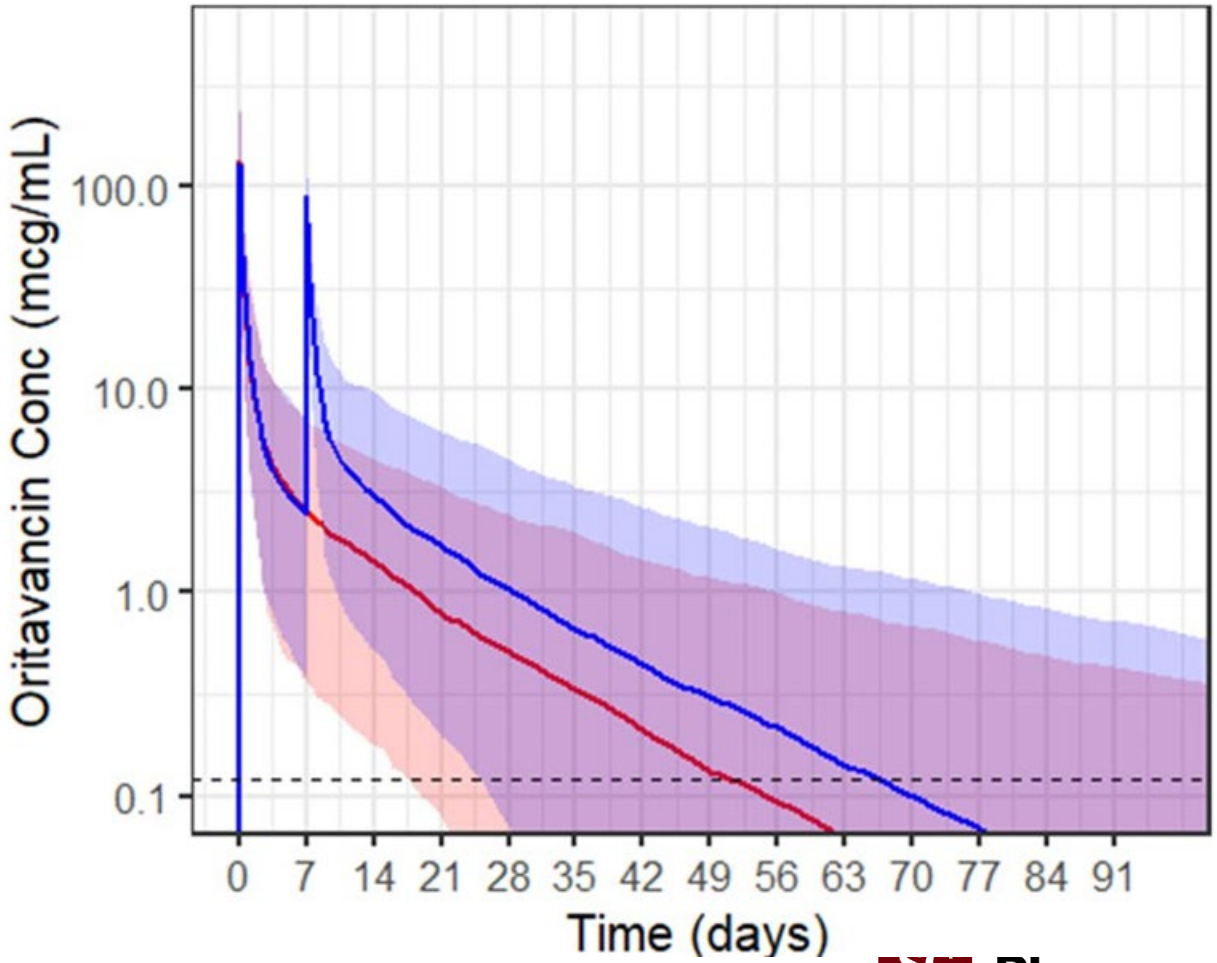


Lehoux D, et al. Antimicrob Agents Chemother 2015;59:6501-6.

DOSING STRATEGIES – ORITAVANCIN

- **1200mg x 1 IV dose followed by 800mg IV dose on day 8** provides sustained oritavancin concentrations (total) above MICs for 8 weeks or for 4.5 weeks (free)

- High AUC/MIC maintained throughout the time evaluation period
  - Some investigators feel that **1200mg x 2 doses (q1 week)** is preferred for sustained concentrations



Rose W, et al. Drugs 2020 Suppl 1:536-40.

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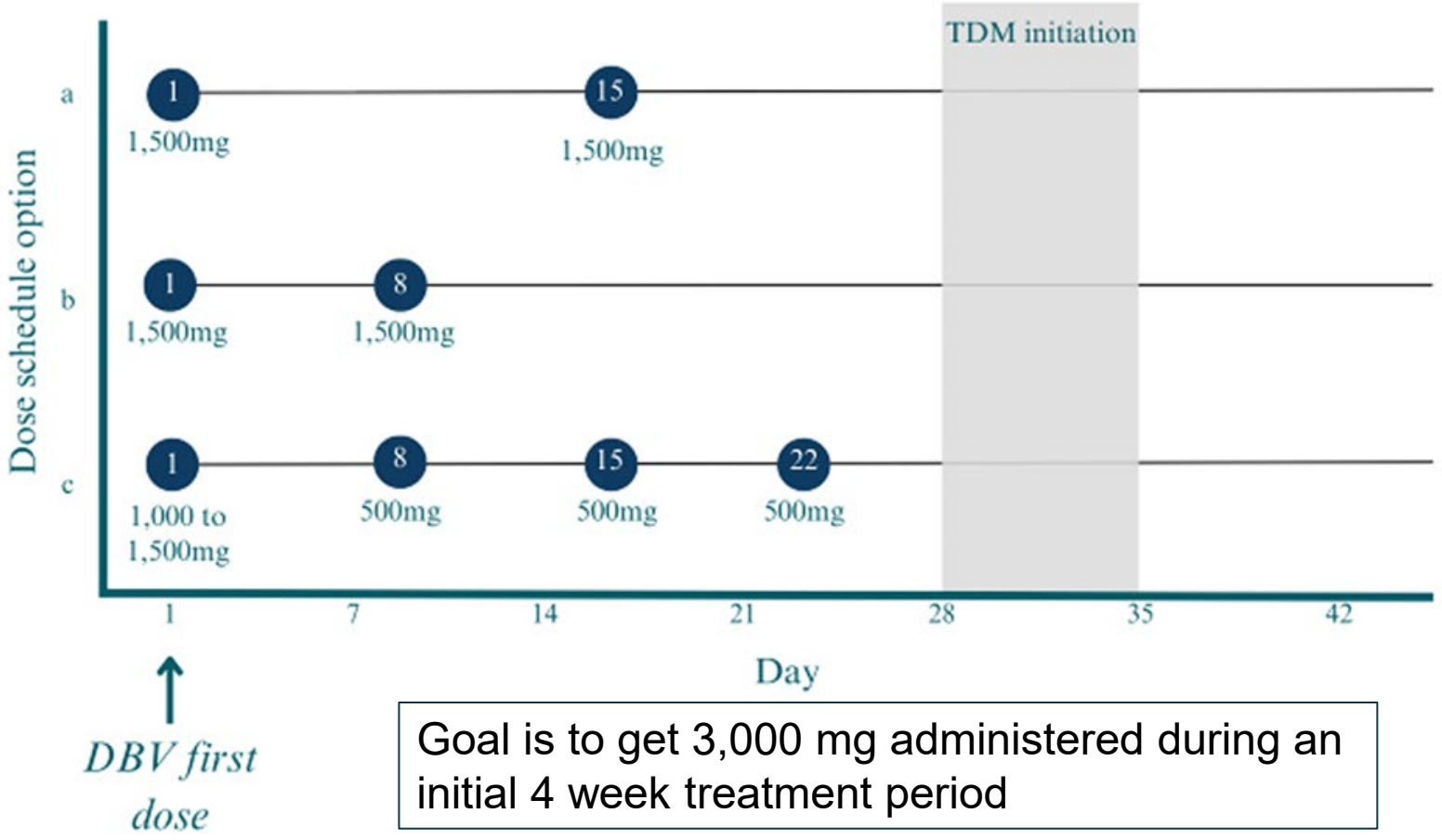
WHAT ABOUT THE UTILITY OF THERAPEUTIC DRUG MONITORING?

- Expert panel assembled in 2023 recommended the use of TDM for treatment durations of dalbavancin over 4 weeks and to consider use if opting for a weekly dosing regimen for 4 to 6 weeks (or longer)
- Guidance suggested to redose at a “trough” of < 8 mcg/mL
- Acknowledged that AUC/MIC was the best predictor of outcomes
- Provided dalbavancin specific recommendations for long-term dosing

Cattaneo D, et al. Antibiotics 2024, 13, 20. https:// doi.org/10.3390/antibiotics13010020

Senneville et al. Int J Antimicrob Agents 2023 (62):5

WHAT ABOUT THE UTILITY OF THERAPEUTIC DRUG MONITORING?



Goal is to get 3,000 mg administered during an initial 4 week treatment period

But how would we do this in South Carolina?

Senneville et al. Int J Antimicrob Agents 2023 (62):5

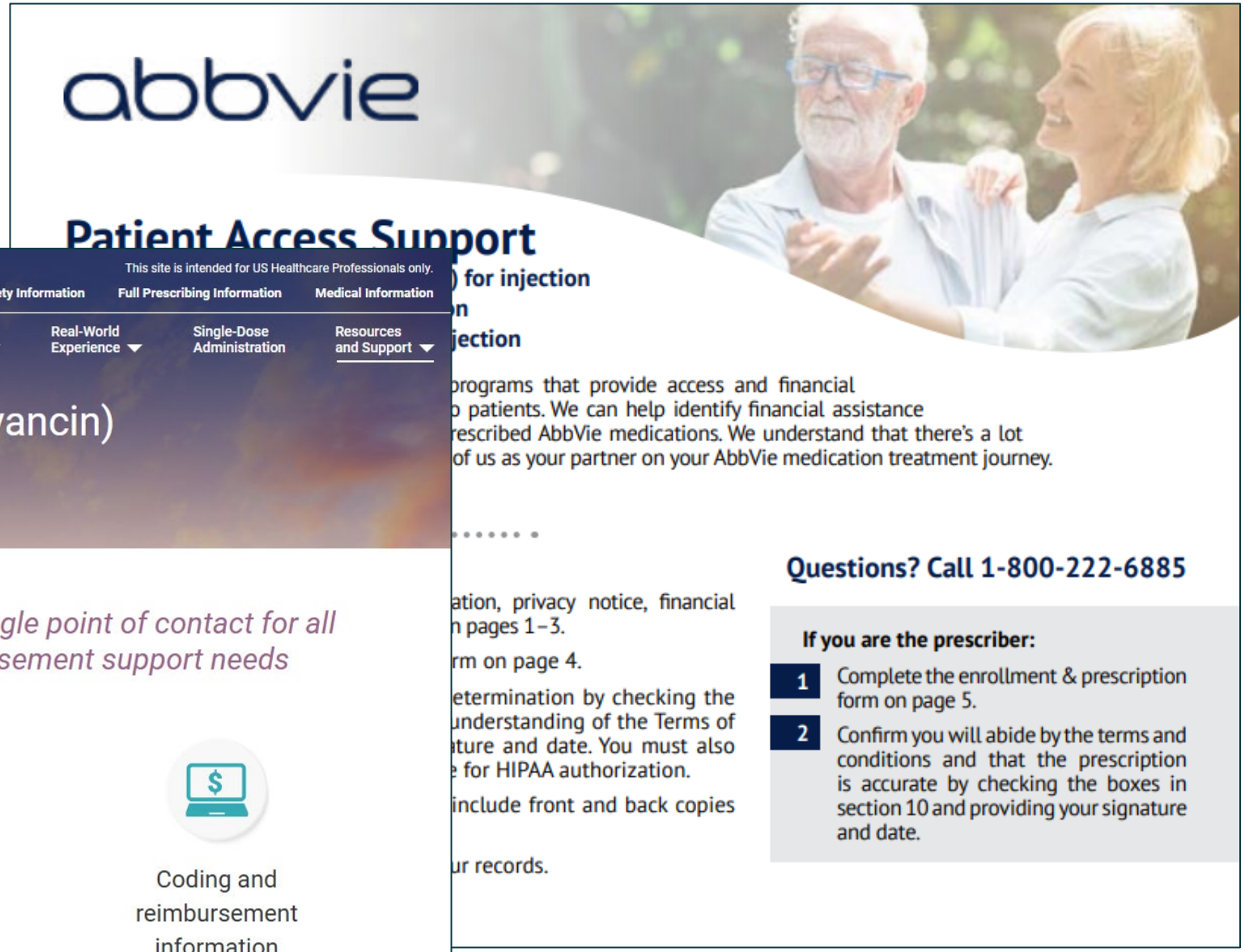
STEWARDING THE COSTLY ANTIBIOTIC

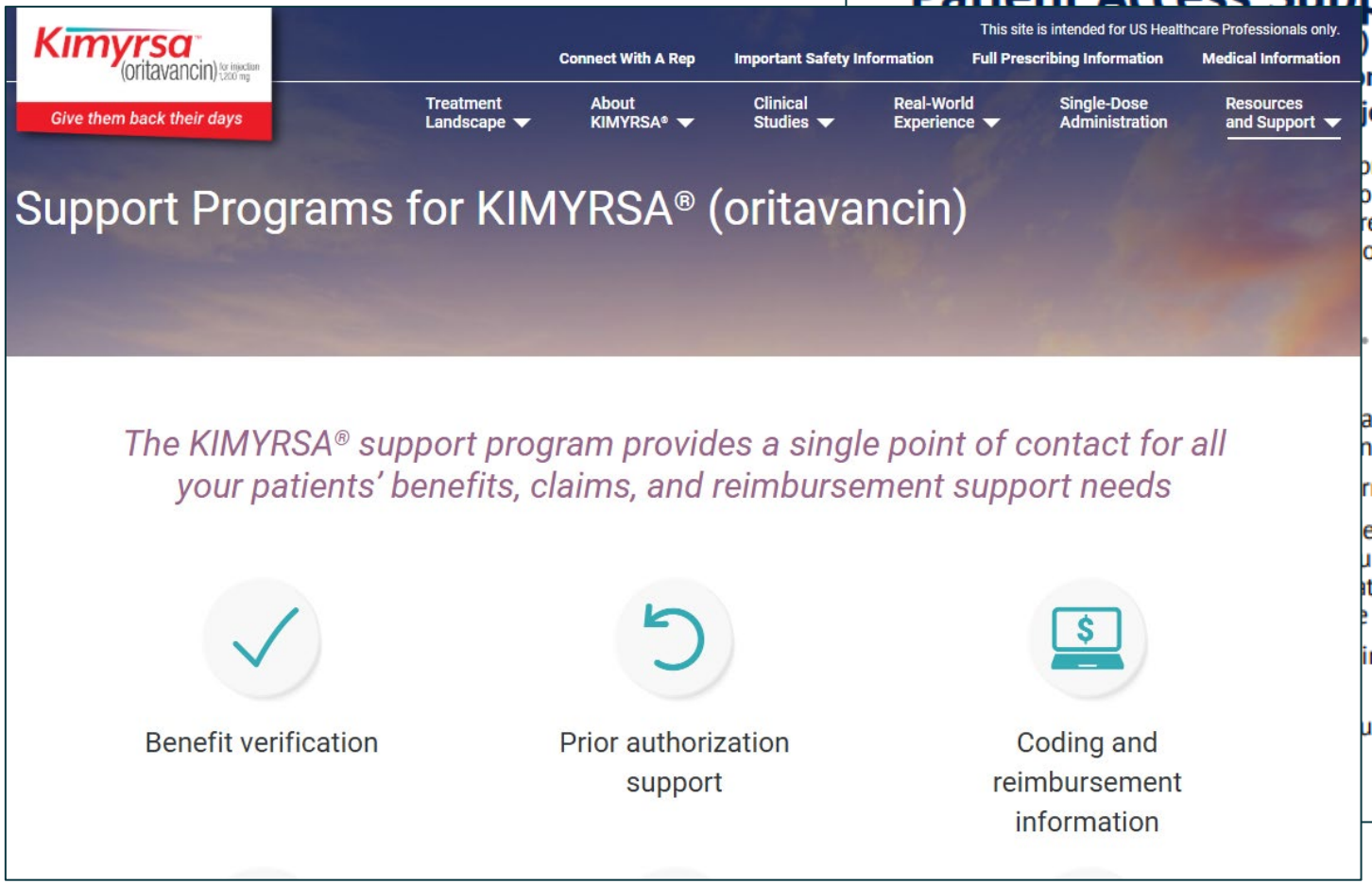
Is it cost-effective to use long-acting lipoglycopeptides?

- Antosz et al.
  - Average of $31,000-$55,000 savings per patient based on line item charges in a matched cohort with SOC among patients unable to use home-health/infusion center or PO alternatives
- Morrissette et al. per patient savings (n=56)
  - $40,455 (IQR: $20,900-$62,700) in persons who use drugs (PWUD) (82% Medicaid)
  - $19,583 (IQR: $15,375-$23,735) in non-PWUD (51% Medicaid, 31% Medicare, 26% Commercial)
- Bouza et al. drug cost savings only (n=69)
  - $3,401 per patient

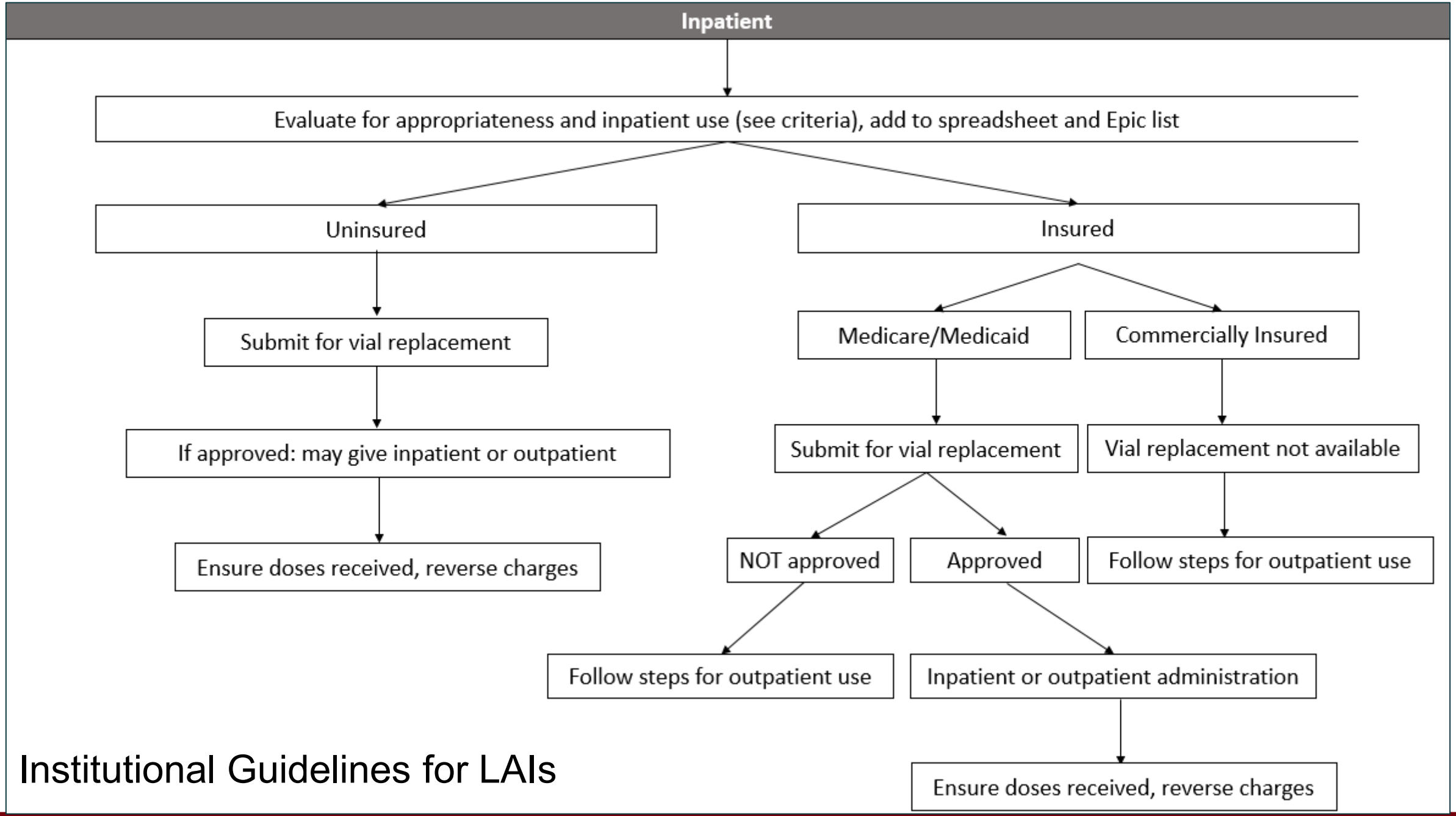
Morrissette T, et al. Open Forum Infect Dis 2019
Bouza E, et al. IJAA 2018
Antosz K, et al. 2023

Leveraging patient assistance programs





Available at: https://www.abbvie.com/patients/patient-support/patient-assistance/eligibility-criteria.html
Available at: https://kimyrsa.com/support-programs



Institutional Guidelines for LAIs

Outpatient

Evaluate for appropriateness (see description), add to spreadsheet and Epic list

Uninsured

Submit for vial replacement

- NOT approved → Cost prohibitive for patient
- Approved → Enter infusion center referral → Enter therapy plan → Call April (803-434-4717) for scheduling → Email Savannah Mancuso → Receive shipment from 1MP → Deliver drug to 5MP for Savannah to pick up → Ensure doses received, reverse charges

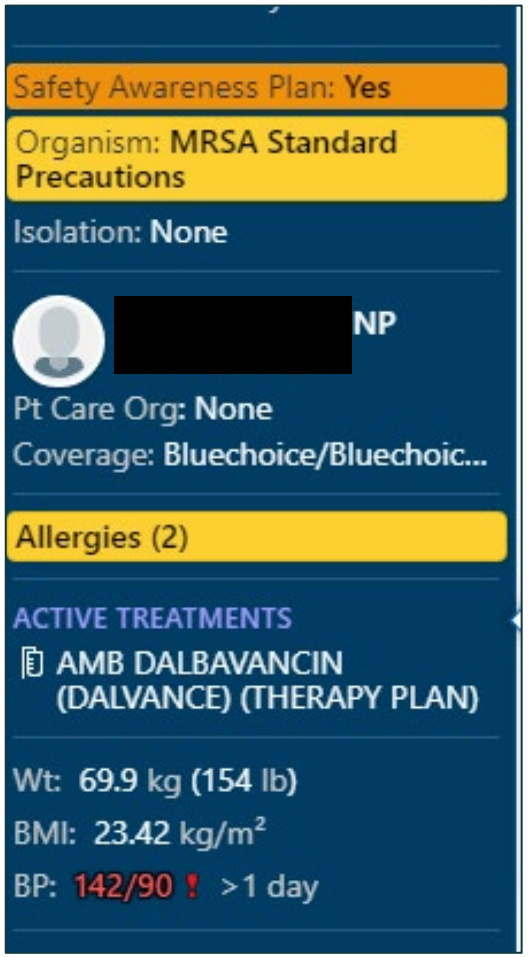
Insured

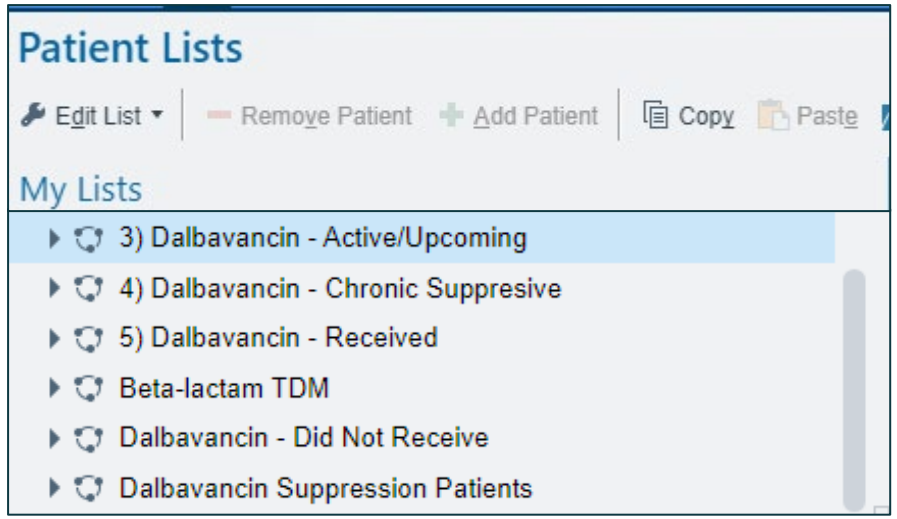
Insurance Type	Typical Approval
Medicare A/B	Approved at infusion center
Medicaid	May need to submit prior authorization[1]
Commercial insurance[2]	May need to submit prior authorization[1]

1. Discuss with Dan/Chad/April → see supplemental
2. Including BCBS

Approval confirmed with insurance (through Dan/Chad/April) → Enter infusion center referral → Enter therapy plan → Call April (803-434-4717) for scheduling → Email Savannah Mancuso → Ensure doses received

LEVERAGING THE EHR





Tracking dalbavancin patients both acutely and longitudinally

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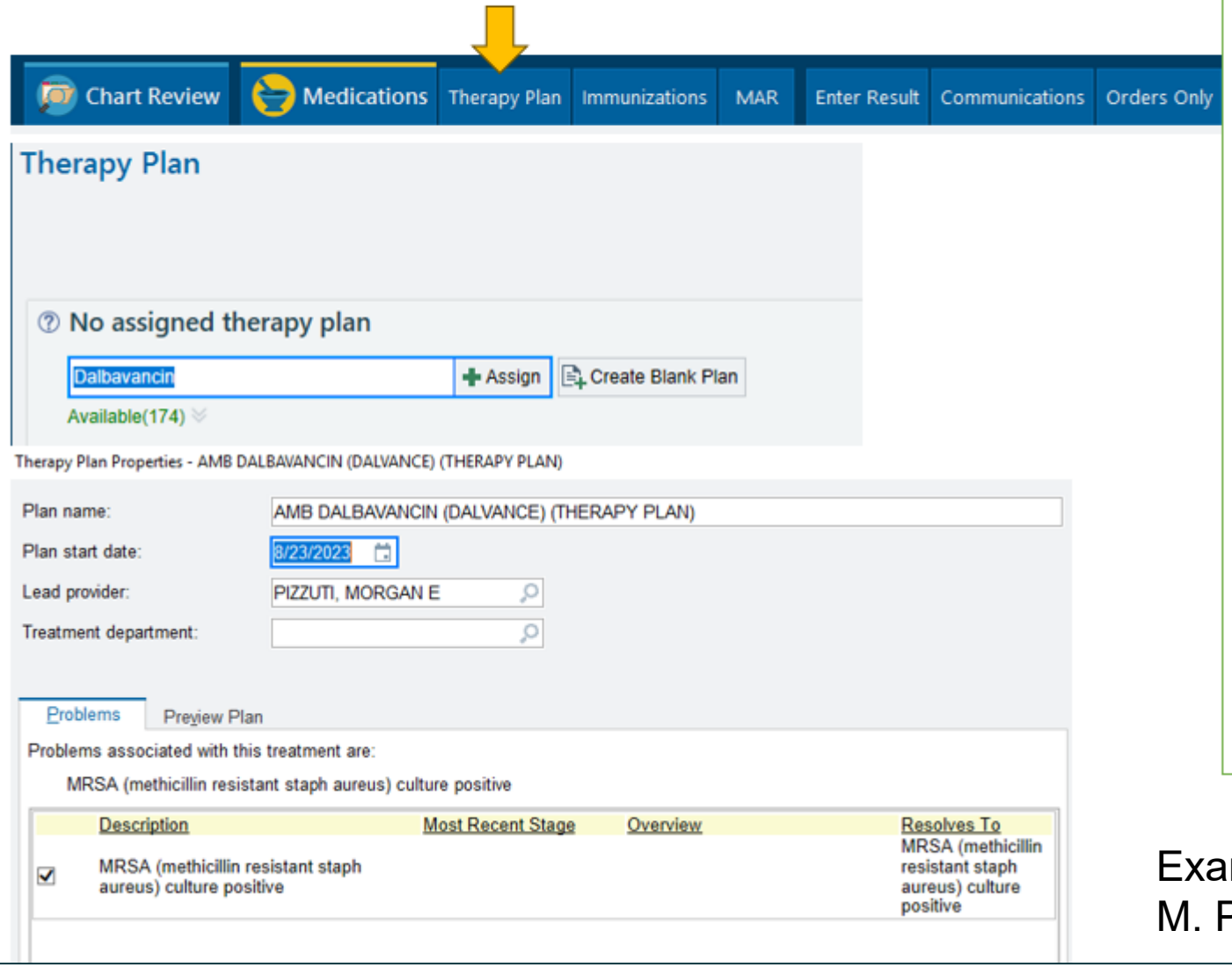
How to Input Therapy Plan



- Select Place Amb Orders
- Next, input therapy plan – if you do not have the Therapy Plan button on your list of selections to choose from, follow these steps:
  - Select the drop-down menu near the wrench on same row as Chart Review
  - Select specialty tools
  - Select Therapy Plan (can star to make a favorite icon to always show up)
- Select Therapy Plan and enter "Dalbavancin"
- Choose a plan start date → if needing scheduling arranged, please allow 3-5 business days for approval and scheduling at the infusion center, select a date that is within this timeframe of when you think the patient would be able to get the dalbavancin
- Select "Assign Plan"

Example of staff education (Courtesy of M. Pizzuti)

REAL-WORLD APPLICATION: LOCAL DECISIONS

- Self-pay/un- or underinsured patients:
  - Vial Replacement Program
  - Whose responsibility to complete paperwork?

- Insured patients:
  - Reimbursement may hinge on timing of infusion --- dated different than discharge
  - Benefits investigation – whose responsibility?

- Other items to consider:
  - Scheduling
  - Transportation
  - Patient reliability – when do we consider doses inpatient vs. outpatient?

Stewarding the costly antibiotic recap

- Establish protocoled use of LA lipoglycopeptides
- 340B eligible reimbursement in outpatient setting
- Prior authorizations may be needed for third party payers

- Justify “net gain” despite inpatient use being unpopular due to poor reimbursement
- Anticipate the need, especially for self-pay patients, difficult barriers to care, leaving AMA
- Ensure patient transportation if using infusion center
- Stress follow-up and verify best contact info

Bookstaver PB, et al. Clin Infect Dis 2021

SOME FINAL PERSONAL THOUGHTS DALBAVANCIN OR ORITAVANCIN

- Not for ABSSSI…feel that patients able to be discharged from the ED should be able to take a low cost, fairly benign oral option
- Not for CNS (we didn't discuss, but likely not a great option, see Nau R, et al. Antibiotics 2024)
- Transitions of care option in patients who have cleared their bacteremia (if bacteremic in first place) especially in those where OPAT or oral antibiotics may not be *optimal*
- Suppression in patients with retained hardware especially those who have not tolerated a first line option
- Need to consider ability to do TDM and to test isolates for susceptibility whenever possible (I'm a fan of local epi data)

FEW KEY REFERENCES TO HELP GUIDE YOU

- Ong SWX, et al. **Unlocking the DOOR-how to design, apply, analyse, and interpret desirability of outcome ranking endpoints in infectious diseases clinical trials**. Clin Microbiol Infect. 2023 Aug;29(8):1024-1030. doi: 10.1016/j.cmi.2023.05.003.
- Tran TT, et al. **New Perspectives on Antimicrobial Agents: Long-Acting Lipoglycopeptides**. Antimicrob Agents Chemother. 2022 Jun 21;66(6):e0261420. doi: 10.1128/aac.02614-20.
- Steuber TD, et al. **Head-to-head comparison of multi-dose oritavancin and dalbavancin for complicated infections: A propensity score-matched analysis**. Int J Antimicrob Agents. 2024 Jun;63(6):107165. doi: 10.1016/j.ijantimicag.2024.107165. Epub 2024 Apr 1. PMID: 38570019.
- Galfo V, Tiseo G, Riccardi N, Falcone M. **Therapeutic drug monitoring of antibiotics for methicillin-resistant Staphylococcus aureus infections: an updated narrative review for clinicians**. Clin Microbiol Infect. 2025 Feb;31(2):194-200. doi: 10.1016/j.cmi.2024.08.021.
- Forrister NM, McCarty TP, Pappas PG. **New Perspectives on Antimicrobial Agents: Rezafungin**. Antimicrob Agents Chemother. 2024 Dec 12:e0064623. doi: 10.1128/aac.00646-23.
- Antosz K, et al. **Clinical Utility and Cost Effectiveness of Long-Acting Lipoglycopeptides Used in Deep-Seated Infections among Patients with Social and Economic Barriers to Care**. Pharmacy (Basel). 2021 Dec 23;10(1):1. doi: 10.3390/pharmacy10010001. PMID: 35076601; PMCID: PMC8788434.
- Turner NA, Hamasaki T, Evans S, et al. **Dalbavancin is non-interior to standard of care therapy for complicated S. aureus bacteremia: Results of the DOTS trial**. Presented at: 34th European Society of Clinical Microbiology and Infectious Diseases (ESCMID); April 27-30, 2024; Barcelona, Spain. Oral Presentation.

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STEWARDING LONG-ACTING INJECTABLE ANTIMICROBIALS FOR POSITIVE PATIENT IMPACT

P. Brandon Bookstaver, PharmD, FCCP, FIDSA, BCIDP

SC Infectious Diseases Society Meeting

Charleston, SC ● January 25, 2025

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