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Rapid Clinical Updates: Striving for Oral Stepdown: Novel Agents and Strategies for Avoiding OPAT

Speakers

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- Duke Center for Antimicrobial Stewardship and Infection, Duke University

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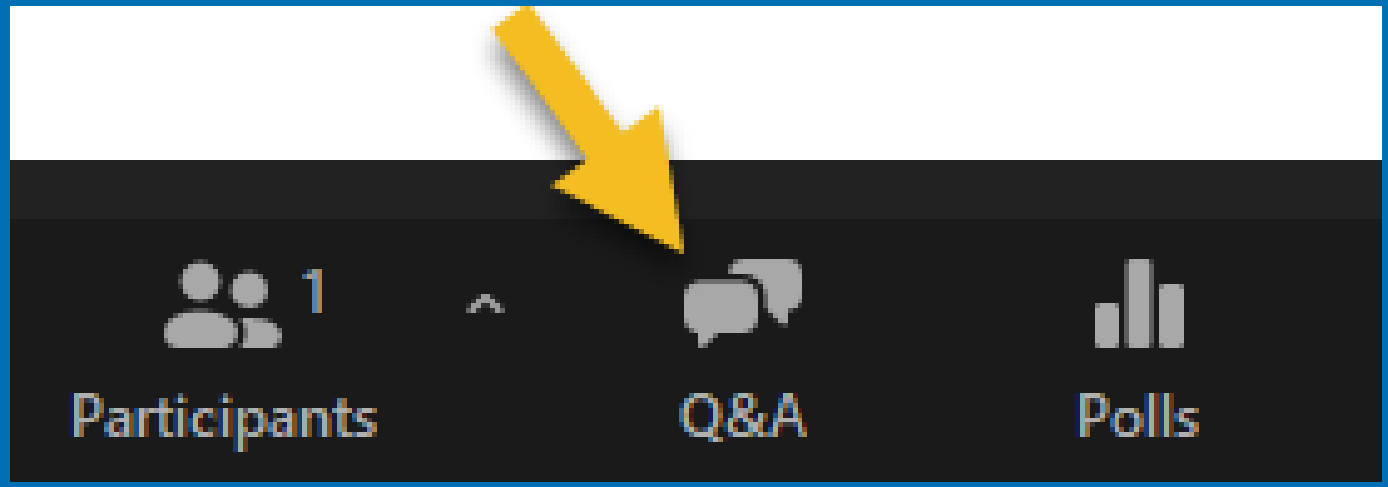
Please submit questions using Q&A feature

We will have Q&A time after



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QUESTIONS

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Question 1

1. **Which of the following therapies has RCT level evidence for the treatment of bloodstream infection?**

    A. Oritavancin
    B. Dalbavancin
    C. Tedizolid
    D. Omadacycline
    E. Eravacycline

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Question 2

2. **Which of the following patients have generally been excluded from studies of oral stepdown therapy?**

   A. Patients with retained infected prosthetic material
   B. Patients with central nervous system involvement
   C. Patients with severe immunocompromise
   D. Patients with left sided endocarditis
   E. All of the above

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Striving for Oral Stepdown: Novel Agents and Strategies for Avoiding OPAT

Jose Mercado and Rey Perez

11/21/24

Disclosures

- **RP:** none
- **JM:** none

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Objectives

- Articulate the benefits of long-acting infusion therapy and early oral stepdown
- Summarize key principles when assessing patient candidacy for early stepdown
- Assess the literature on new therapeutics of significance

Outpatient Parenteral Antibiotic Therapy (OPAT)

- Prolonged antibiotic therapy has been the historical standard of care for severe infections but comes with numerous downsides:
  - Line associated complications
  - Logistical challenges of placement or patient self-administration
  - High cost of home infusion services or rehab stay
  - Prolonged hospital stay to facilitate coordination
  - Administrative burden of therapeutic drug monitoring

A New Way Forward?

Articles

Efficacy and safety of an early oral switch in low-risk *Staphylococcus aureus* bloodstream infection (SABATO): an international, open-label, parallel-group, randomised, controlled, non-inferiority trial

Prof Achim J Kaasch MD [a], Luis Eduardo López-Cortés MD [b d], Prof Jesús Rodríguez-Baño MD [b d], Prof José Miguel Cisneros MD [c d], M Dolores Navarro MD [c d], Prof Gerd Fätkenheuer MD [e], Norma Jung MD [e], Prof Siegbert Rieg MD [h], Raphaël Lepeule MD [i], Laetitia Coutte MD [i], Prof Louis Bernard MD [j], Adrien Lemaignen MD [j], Katrin Kösters MD [k], Prof Colin R MacKenzie MD [l], Alex Soriano MD PhD [m], Stefan Hagel MD [n], Prof Bruno Fantin MD [o], Matthieu Lafaurie MD [p], Jean-Philippe Talarmin MD [q], Aurélien Dinh MD [r]...Violaine Tolsma

Trials. 2022 May 16;23(1):407. doi: 10.1186/s13063-022-06370-1.

Dalbavancin as an option for treatment of S. aureus bacteremia (DOTS): study protocol for a phase 2b, multicenter, randomized, open-label clinical trial

Nicholas A Turner [1], Smitha Zaharoff [2], Heather King [3 4], Scott Evans [5], Toshimitsu Hamasaki [5], Thomas Lodise [6], Varduhi Ghazaryan [7], Tatiana Beresnev [7], Todd Riccobene [8], Rinal Patel [8], Sarah B Doernberg [9], Urania Rappo [10], Vance G Fowler Jr [1], Thomas L Holland [11]; Antibacterial Resistance Leadership Group (ARLG)

Affiliations + expand

PMID: 35578360 PMCID: PMC9109297 DOI: 10.1186/s13063-022-06370-1

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

Authors: Ho-Kwong Li, M.R.C.P., Ines Rombach, D.Phil., Rhea Zambellas, M.Sc., A. Sarah Walker, Ph.D., Martin A. McNally, F.R.C.S.(Orth.), Bridget L. Atkins, F.R.C.P., Benjamin A. Lipsky, M.D., +52, for the OVIVA Trial Collaborators* Author Info & Affiliations

Published January 30, 2019 | **N Engl J Med 2019;380:425-436** | **DOI: 10.1056/NEJMoa1710926** | **VOL. 380 NO. 5**

ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Authors: Kasper Iversen, M.D., D.M.Sc., Nikolaj Ihlemann, M.D., Ph.D., Sabine U. Gill, M.D., Ph.D., Trine Madsen, M.D., Ph.D., Hanne Elming, M.D., Ph.D., Kaare T. Jensen, M.D., Ph.D., Niels E. Bruun, M.D., D.M.Sc., +13, and Henning Bundgaard, M.D., D.M.Sc. Author Info & Affiliations

Published August 28, 2018 | **N Engl J Med 2019;380:415-424** | **DOI: 10.1056/NEJMoa1808312** | **VOL. 380 NO. 5**

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Antimicrobial Stewardship

Antibiotics with high oral bioavailability can minimize unnecessary indwelling vascular lines and risks of CLABSIs

Antibiotics with long half-lives allow for simplified dosing regimens which reduces risk of non-adherence, which is a key contributor to antibiotic resistance

Antibiotics with long half lives can achieve steady drug levels and reduce the risk of subtherapeutic dosing

- Reduce unnecessary antibiotic exposure with shorter treatment courses

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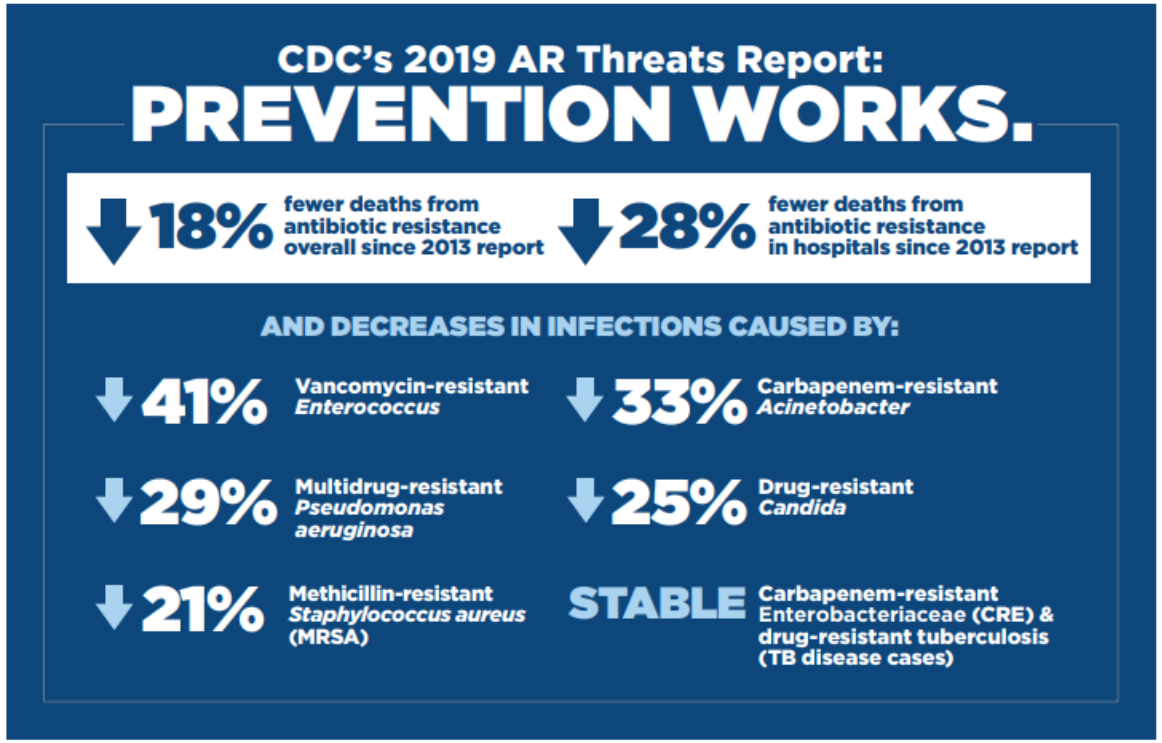
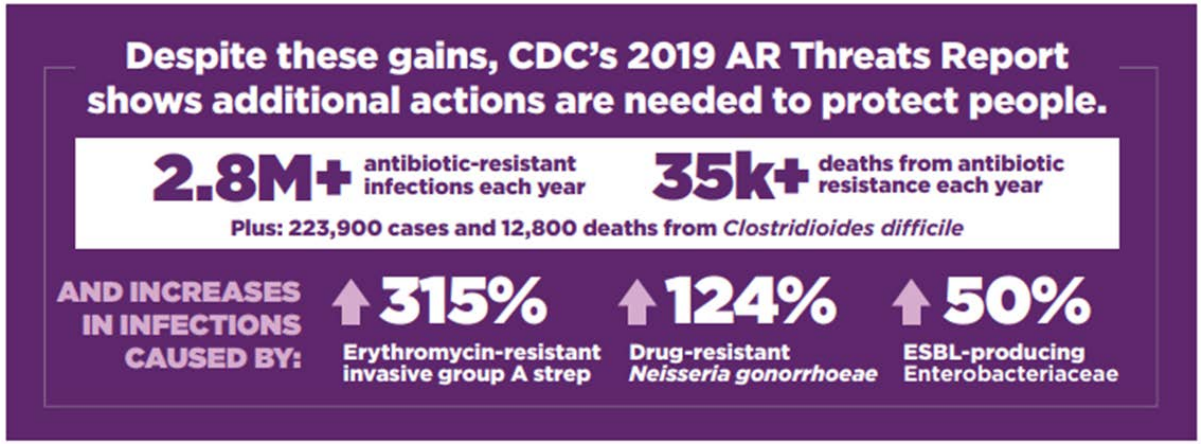
CDC Antibiotic Resistance Threats Report





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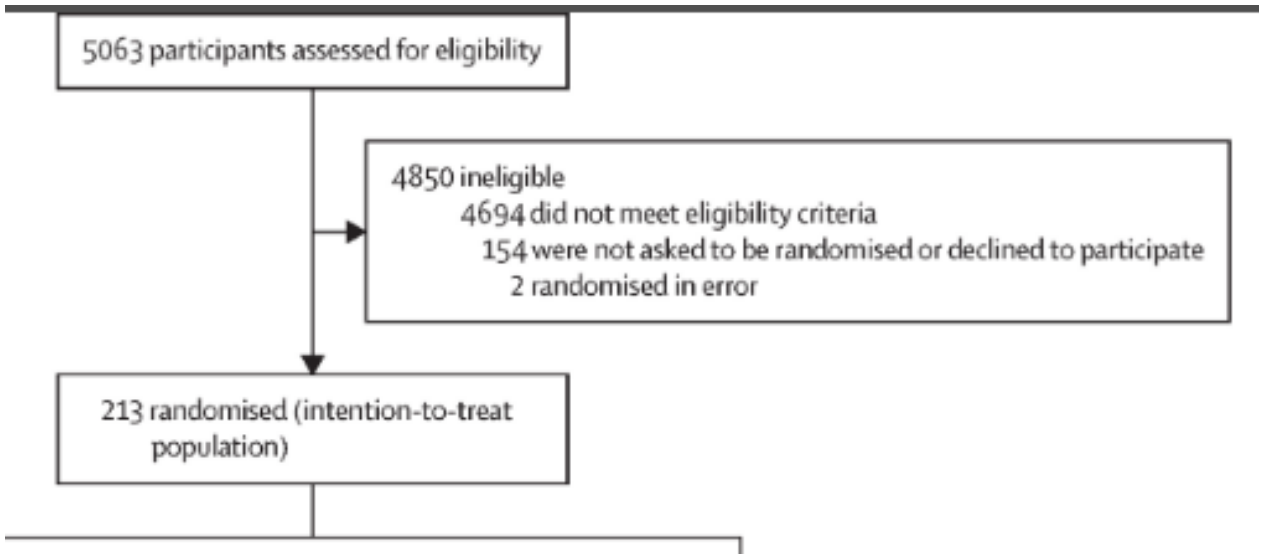
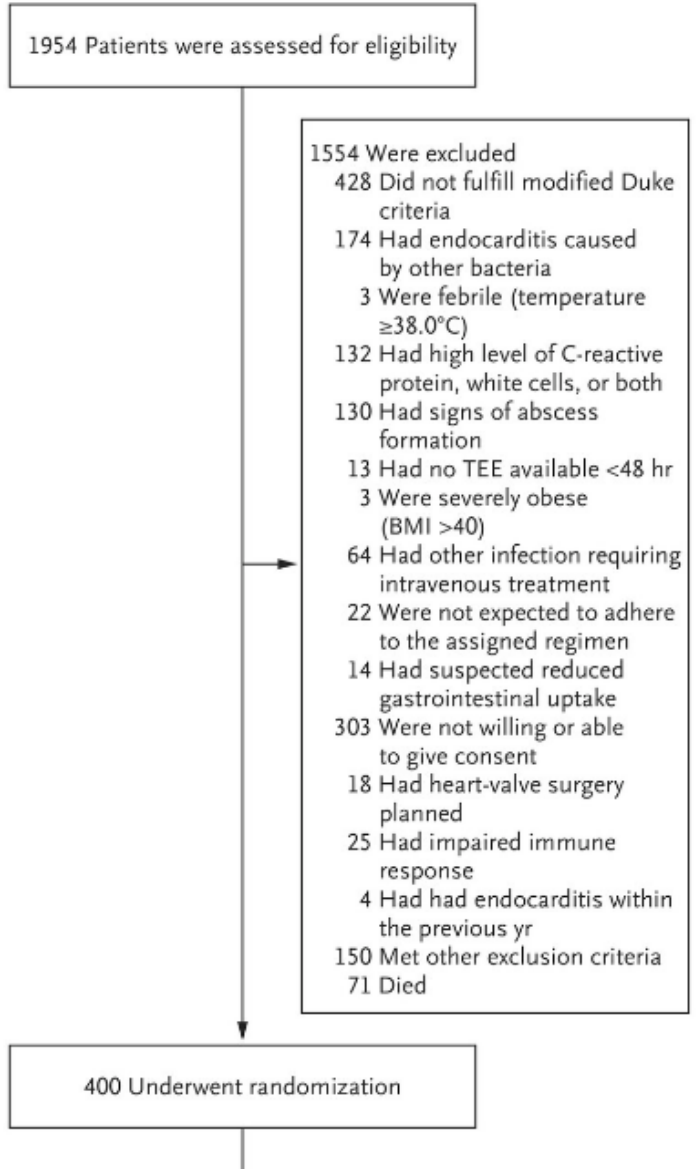
Choosing the right patients



SABATO, Fig 1



POET, Fig 1

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Key Principles: Patient Factors

- Remember the 60-90 Rule
  - Infections due to susceptible isolates respond to appropriate therapy ~90% of the time, whereas infections due to resistant isolates (or infections treated with inappropriate antibiotics) respond ~60% of the time
- Gut Absorption
  - Hx of gastric bypass?
  - DDIs with supplements or PPIs?
- Prosthetic Material
- Severe Immunosuppression

Key Principles: Drug Factors

- Oral bioavailability
- Dose equivalence / augmentation
- Drug penetration to protected sites
- Long term tolerability

Long Acting Infusion Therapies

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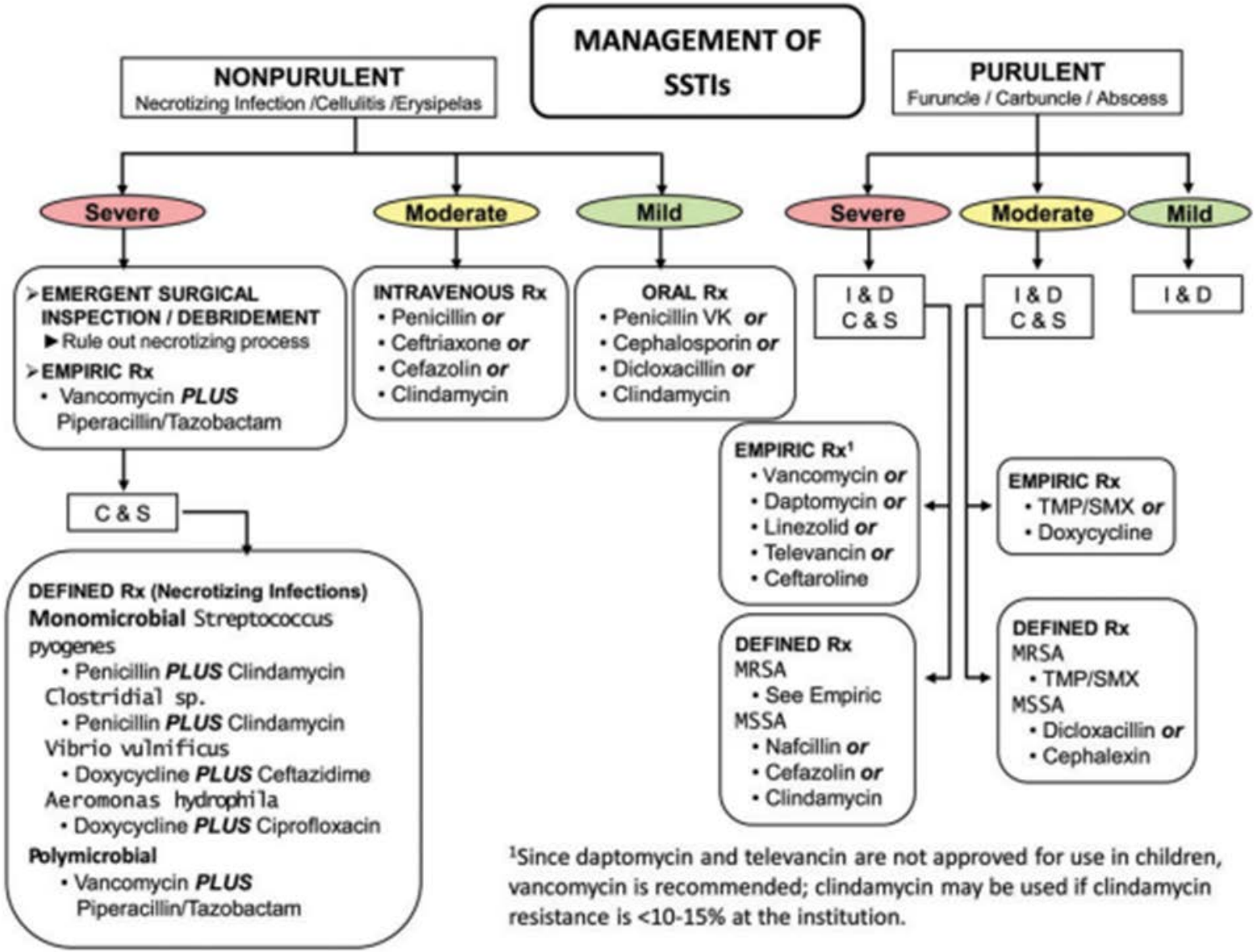
CDC estimated 323,700 cases & 10,600 deaths due to MRSA in 2019



Clinical Infectious Diseases, Volume 59, Issue 2, 15 July 2014, Pages e10–e52, https://doi.org/10.1093/cid/ciu296

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Dalbavancin

Gram-positive microorganisms: *Staphylococcus aureus, Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus dysgalactiae, Streptococcus anginosus group, and Enterococcus faecalis (vancomycin susceptible isolates).*

Dosage in Adult Patients (2.1, 2.3):		
Estimated Creatinine Clearance (CLcr)	**Single Dose Regimen**	**Two-Dose Regimen**
30 mL/min and above or on regular hemodialysis	1500 mg	1000 mg followed one week later by 500 mg
Less than 30 mL/min and not on regular hemodialysis	1125 mg	750 mg followed one week later by 375 mg

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Dalbavancin

No significant difference in clinical treatment success, microbiologic success, and tolerability

- Lower likelihood of experiencing AE than linezolid
- Lower likelihood of experiencing SAE than vancomycin and daptomycin
- **Lower risk of all-cause mortality than vancomycin, linezolid and tigecycline**

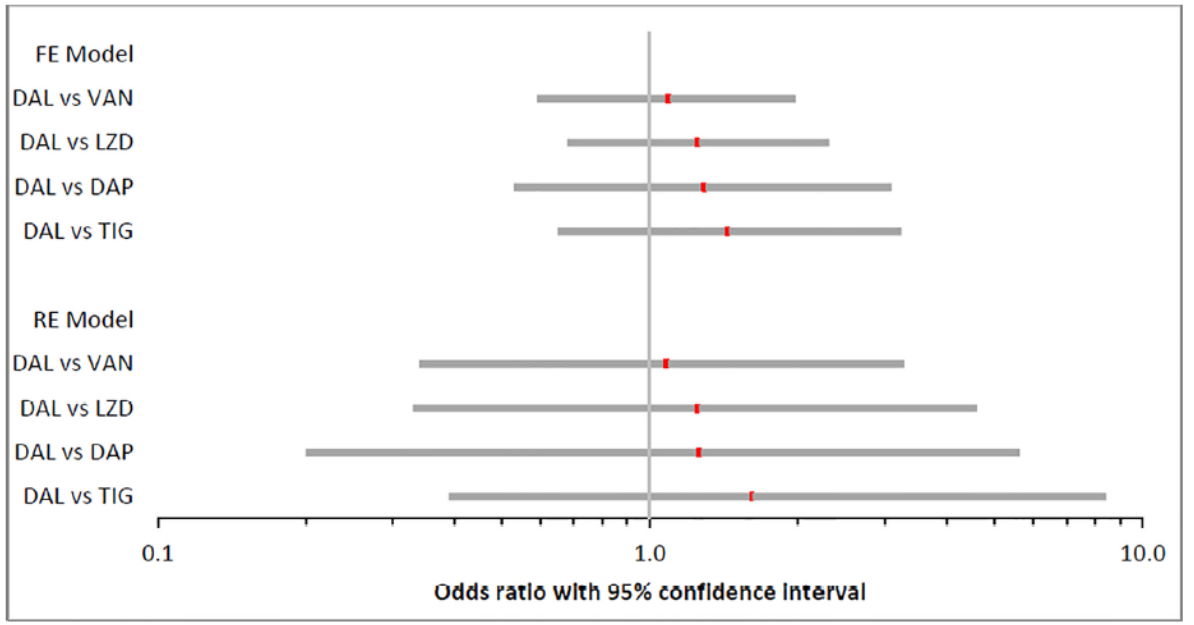

Fig 3. Forest plot on a log scale of the Odds ratios between dalbavancin and all other treatments for discontinuation due to AEs/SAEs for adults only (Odds ratio >1 favours DAL).

https://doi.org/10.1371/journal.pone.0187792.g003

RESEARCH ARTICLE

Comparative efficacy and safety of antibiotics used to treat acute bacterial skin and skin structure infections: Results of a network meta-analysis

Julian F. Guest[1,2]*, Jaime Esteban[3], Anton G. Manganelli[4], Andrea Novelli[5], Giuliano Rizzardini[6,7], Miquel Serra[4]

PLoS ONE 12(11): e0187792. https://doi.org/ 10.1371/journal.pone.0187792

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Dalbavancin

The net cost, calculated as revenue minus total cost, was -$1685 with dalbavancin vs $75 with SoC

Higher 30-day readmission rate

Dalbavancin does not offer an economic or efficacy advantage

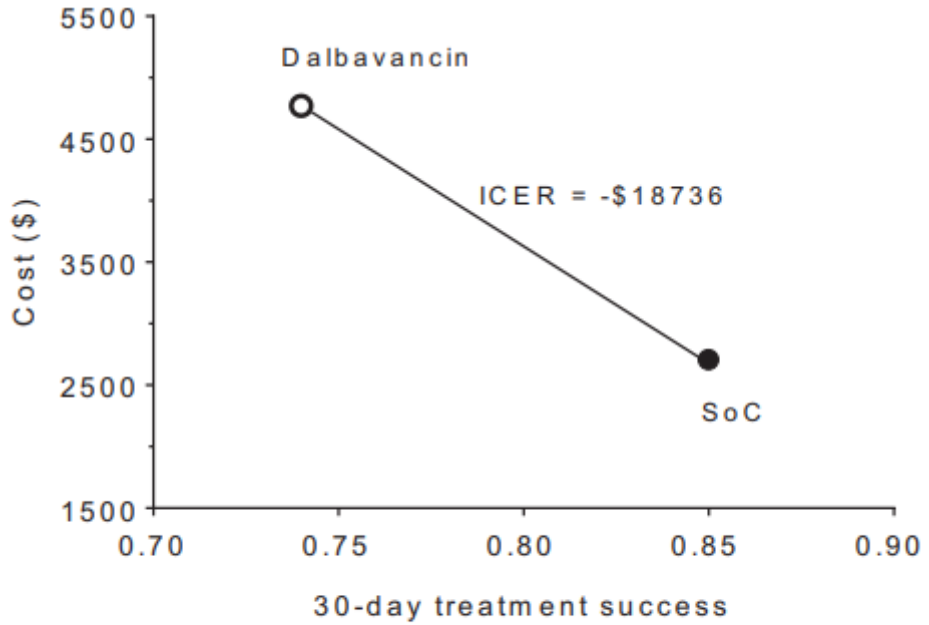

Figure 2. Thirty-day treatment success incremental cost-effectiveness ratio. Abbreviations: ICER, incremental cost-effectiveness ratio; SoC, standard of care.

Clinical Infectious Diseases

MAJOR ARTICLE

Cost-Consequence Analysis of Single-Dose Dalbavancin Versus Standard of Care for the Treatment of Acute Bacterial Skin and Skin Structure Infections in a Multisite Healthcare System

Julia Gonzalez,[1] Diana Carolina Andrade,[1] and JianLi Niu[2]

[1]Department of Pharmacy, Memorial Hospital West, Pembroke Pines, Florida, USA, and [2]Office of Human Research, Memorial Healthcare System, Hollywood, Florida, USA

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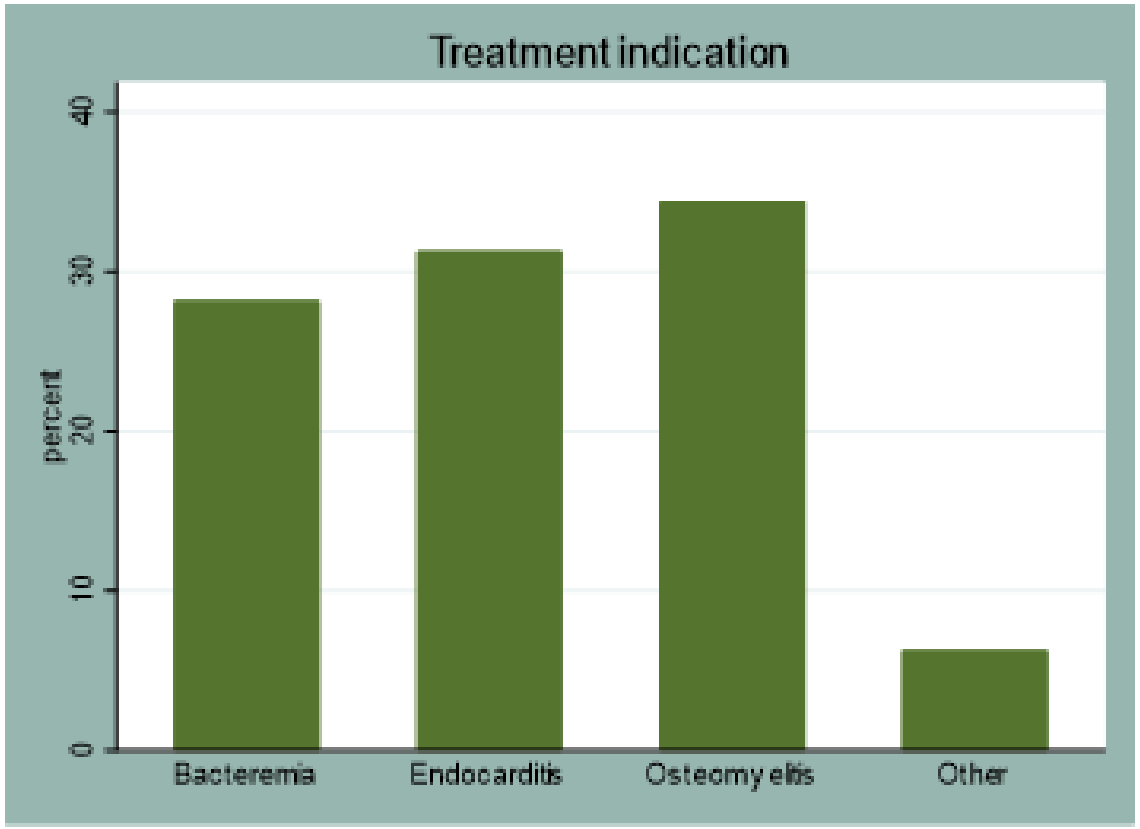
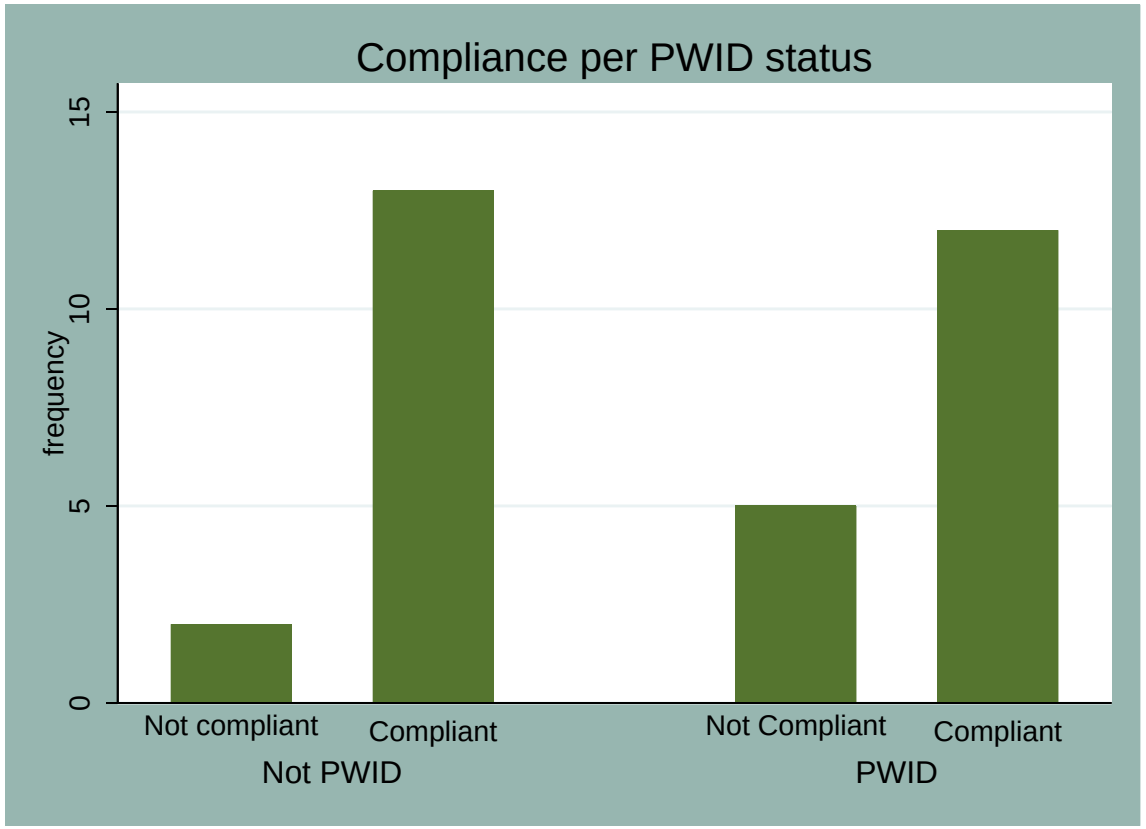
Dalbavancin





Dalbavancin Utilization in Rural Healthcare Setting: A Single Center Three Years' Experience
Ahmad AlSalman, MD, Craig Worby, PharmD, Ritika Zijoo, MD, Emma Considine, DO, Colleen Kershaw, MD

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Table 6 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%)

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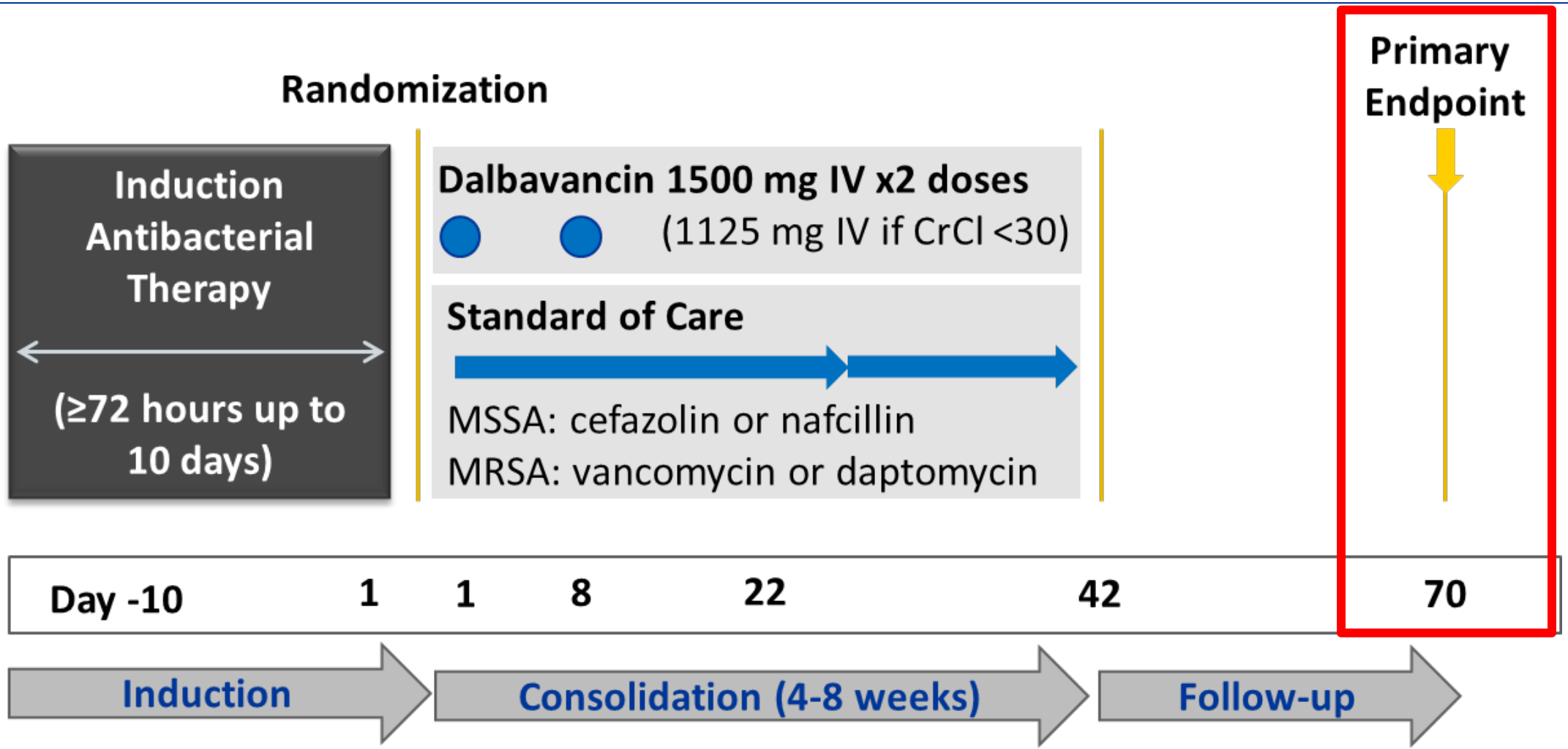
Gatti M, Andreoni M, Pea F, Viale P. Real-World Use of Dalbavancin in the Era of Empowerment of Outpatient Antimicrobial Treatment: A Careful Appraisal Beyond Approved Indications Focusing on Unmet Clinical Needs. Drug Des Devel Ther. 2021 Aug 3;15:3349-3378. doi: 10.2147/DDDT.S313756. PMID: 34376971; PMCID: PMC8349200.

DOTS Trial

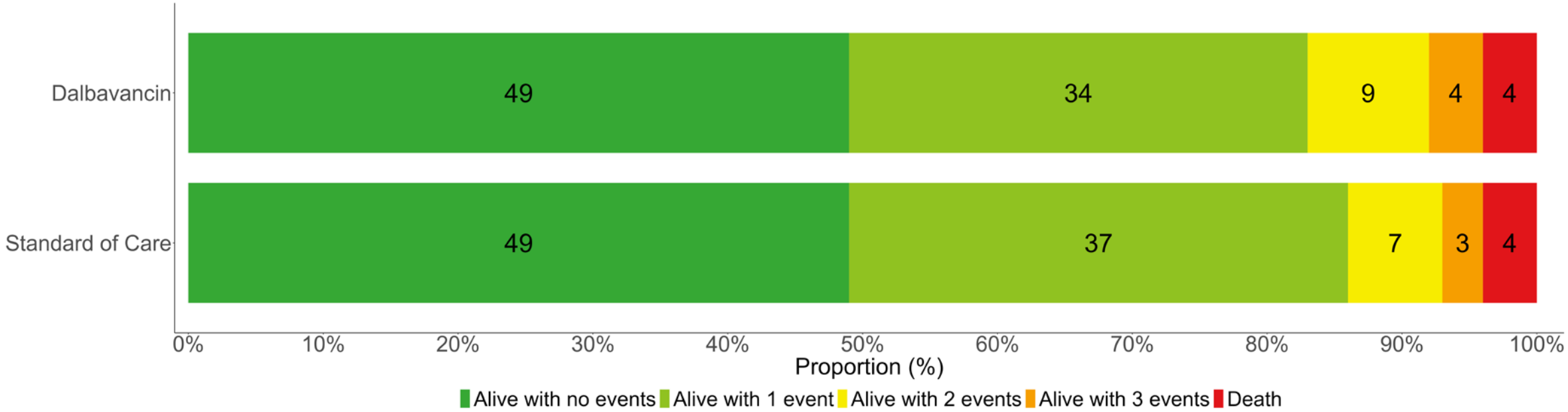
- Goal was to evaluate the efficacy and safety of dalbavancin versus standard of care for treatment of complicated SAB and right sided endocarditis
- Open label, multicenter randomized controlled trial
- Excluded patients with CNS involvement, left sided endocarditis, retained infected prosthetic material and severe immune compromise
- Primary outcome utilized a desirability of outcome analysis

METHODS (1): DOTS Study Design



Turner et al *Trials* 2022; PMID: 35578360

RESULTS (6): Primary Outcome
Overall DOOR Distribution



DOOR probability: 47.7% (95% CI: 39.8%-55.7%)

Conclusion: Benefits/risks similar with dalbavancin vs SOC

RESULTS (8): Secondary Outcomes
Non-inferiority Analysis

	Dalbavancin (n=100)	Standard of Care (n=100)
Clinical efficacy (95% CI)	73% (64-82)	72% (63-81)
Difference (95% CI)	**+1% (-12 to +14%)**	

Conclusion: Dalbavancin is non-inferior to SOC by traditional clinical efficacy

RESULTS (9): Safety

Adverse Events (AEs)	Dalbavancin (n=100)	Standard of care (n=100)
Serious adverse events (SAEs)	43	37
Related serious AEs	2	4
AEs leading to discontinuation	3	12

-Overall similar AE rates
-Slightly more AEs leading to discontinuation with SOC

Oritavancin

Results

Demonstrates comparable efficacy to Vancomycin

Reduced occurrence of treatment related AE when compared to Vancomycin

Considerations

Lower rate of additional post-treatment oral and IV antibiotics

More effective in reducing rate of 30 day ER visits

More likely to reduce 30 day readmissions rate

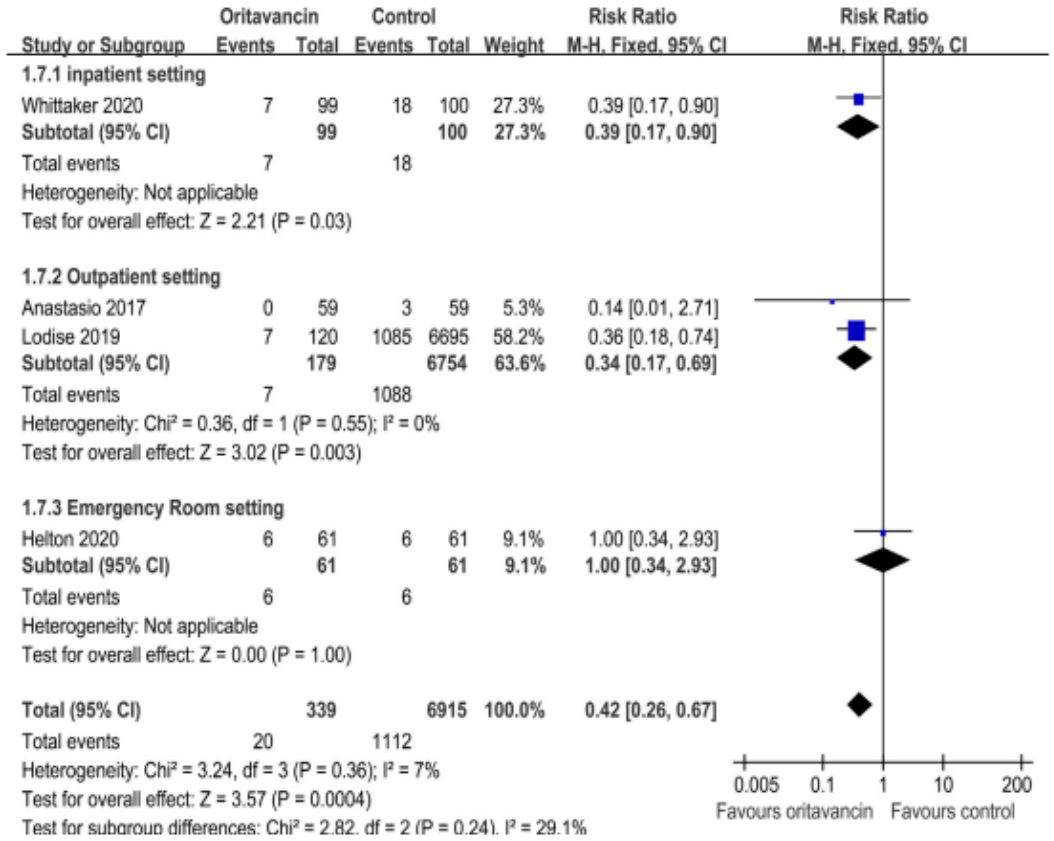


Fig. 9. Forest plots showing risk ratio with 95% confidence interval (CI) of 30-day readmission rates in a fixed-effects model.

Review

Efficacy and safety of oritavancin for the treatment of acute bacterial skin and skin-structure infections: a systematic review and meta-analysis

Huan Zhang[a,b], Weiying Zhou[b], Jin Wang[a], Yun Cai[a,*]

Journal of Global Antimicrobial Resistance 25 (2021) 380–389

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Oritavancin

Outcomes	Oritavancin	Vancomycin	*P* Value
Unadjusted Outcomes			
30 day subsequent admission rates	5.80%	16.20%	.002
Mean healthcare costs	$10 096 (8865)	$12 779 (28 773)	.30
Adjusted Outcomes			
30 day subsequent admission rates	6.10%	16.20%	.003
Mean healthcare costs	$12 695	$12 717	.98

Open Forum Infectious Diseases

MAJOR ARTICLE

Comparisons of 30-Day Admission and 30-Day Total Healthcare Costs Between Patients Who Were Treated With Oritavancin or Vancomycin for a Skin Infection in the Outpatient Setting

Thomas P. Lodise,[1] Christina Palazzolo,[1] Kerry Reksc,[1] Elizabeth Packnett,[2] and Mark Redell[3]

[1]Albany College of Pharmacy and the Health Sciences, Albany, New York; [2]IBM Watson Health, Bethesda, Maryland, and [3]Melinta Therapeutics, Medical Affairs, Morristown, New Jersey

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Rezafungin

- Long acting echinocandin administered as a once weekly infusion for the treatment of invasive candidal infections
- Similar efficacy and safety profile to standard echinocandins (caspofungin, micafungin, etc)

Table 2 Summary of efficacy data (mITT population, unless otherwise stated)

		Rezafungin (n=139)	Caspofungin (n=155)	Treatment difference (95% CI)
Primary pooled efficacy endpoint: day 30 all-cause mortality				
Deceased or unknown survival status		26 (19%)	30 (19%)	..
	Known deceased	21 (15%)	25 (16%)	..
	Unknown survival status	5 (4%)	5 (3%)	..
Alive		113 (81%)	125 (81%)	..
Death rate*		..	..	−1·5% (−10·7 to 7·7)
Day 14 mycological response				
	Eradication	100 (72%)	106 (68%)	..
	Failure or indeterminate	39 (28%)	49 (32%)	..
	Eradication rate*	..	..	4·3% (−6·2 to 14·7)

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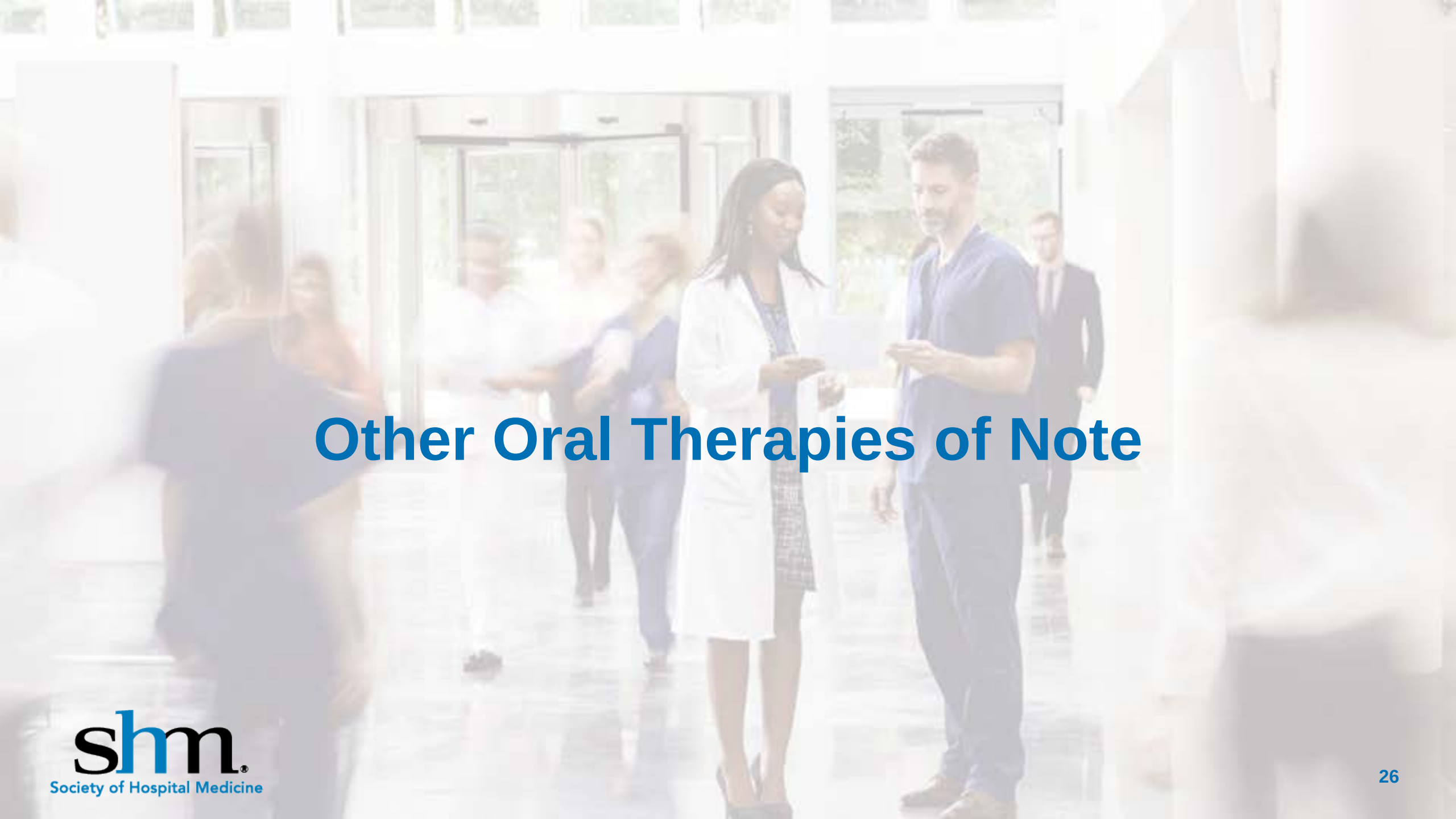

Other Oral Therapies of Note

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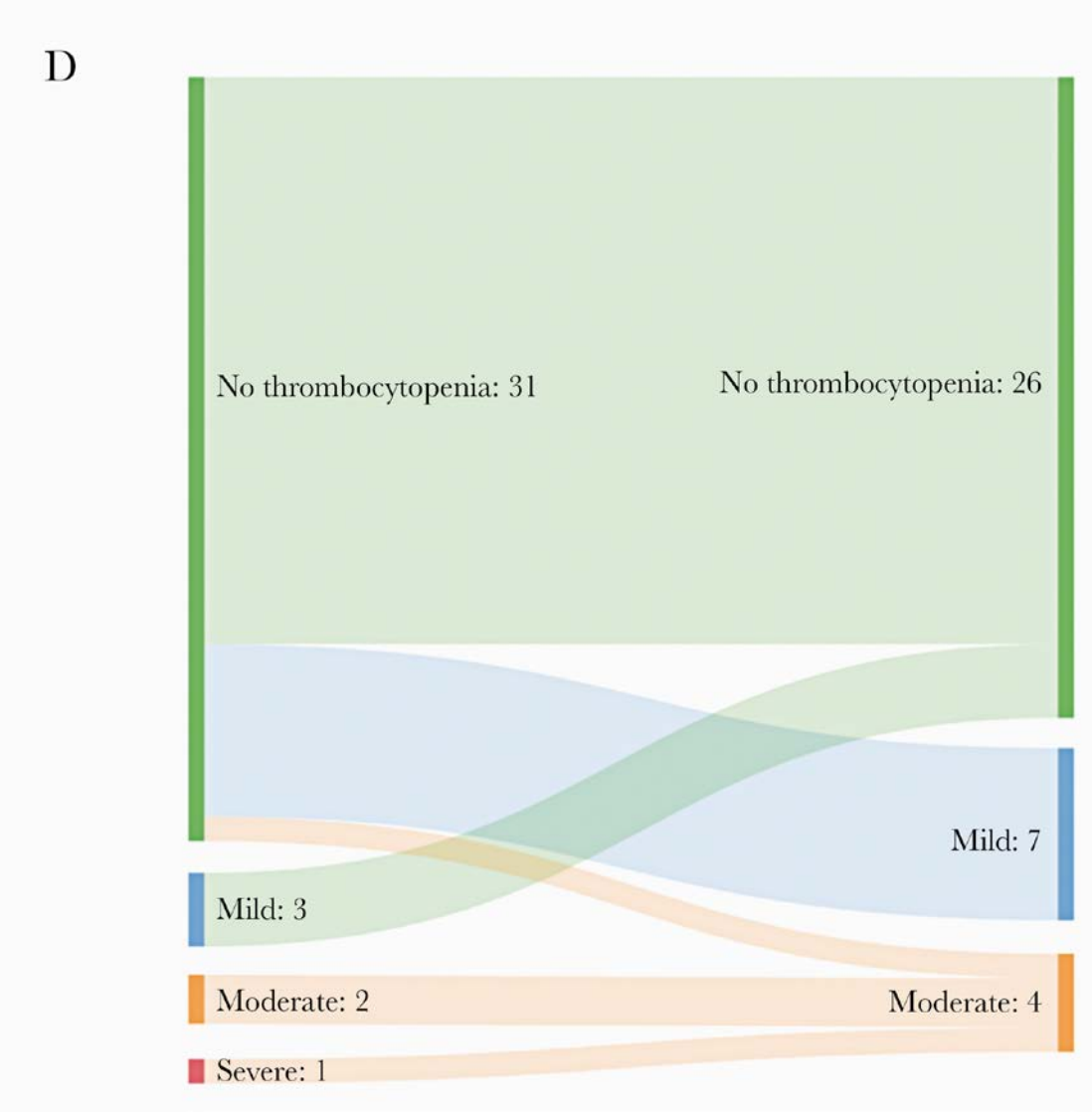
Tedizolid

- Same spectrum of activity as linezolid but daily dosing and with improved tolerability
- Fewer discontinuations for cytopenia, fewer DDIs with serotonergic agents, less peripheral neuropathy
- Poor CNS penetration, poor blood serum penetration as highly protein bound



Open Forum Infect Dis, Volume 9, Issue 6, June 2022, ofac028, https://doi.org/10.1093/ofid/ofac028

Omadacycline

Gram positive organisms:

Staphylococcus aureus (methicillin-susceptible and -resistant isolates),

Staphylococcus lugdunensis,

Streptococcus pyogenes,

Streptococcus anginosus grp. (includes S. anginosus, S. intermedius, and S. constellatus),

Infection	Loading Doses	Maintenance Dose
CABP	NUZYRA Injection: Day 1: 200 mg by intravenous infusion over 60 minutes **OR** 100 mg by intravenous infusion over 30 minutes twice (2.2) **OR** NUZYRA Tablets: Day 1: 300 mg orally twice (2.2)	NUZYRA Injection: 100 mg by intravenous infusion over 30 minutes once daily **OR** NUZYRA Tablets: 300 mg orally once daily(2.2)
ABSSSI	NUZYRA Injection: Day 1: 200 mg by intravenous infusion over 60 minutes **OR** 100 mg by intravenous infusion over 30 minutes twice (2.3) **OR** NUZYRA Tablets: Day 1 and Day 2: 450 mg orally once daily (2.3)	NUZYRA Injection: 100 mg by intravenous infusion over 30 minutes once daily **OR** NUZYRA Tablets: 300 mg orally once daily (2.3)

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Omadacycline

Results

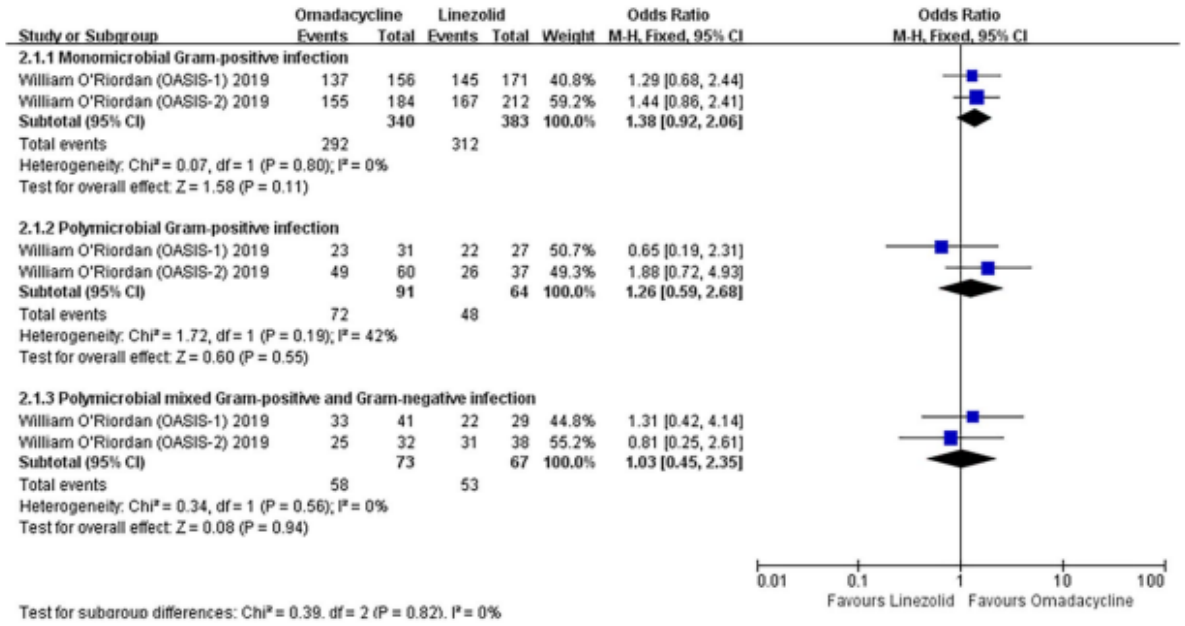
OMC was as good as LZD regarding clinical efficacy and microbiological response, and has a similar safety profile

No significant difference in mortality

Considerations

cSSTIs secondary to **mixed infections**

AEs associated with the long-term use of LZD (**myelosuppression, peripheral and optic neuropathy, serotonin syndrome)**



Efficacy and safety of omadacycline for treating complicated skin and soft tissue infections: a meta-analysis of randomized controlled trials

Wenxin Liang[1†], Hong Yin[2†], Huiling Chen[1], Juan Xu[1*] and Yun Cai[1*]

BMC Infectious Diseases (2024) 24:219 https://doi.org/10.1186/s12879-024-09097-3

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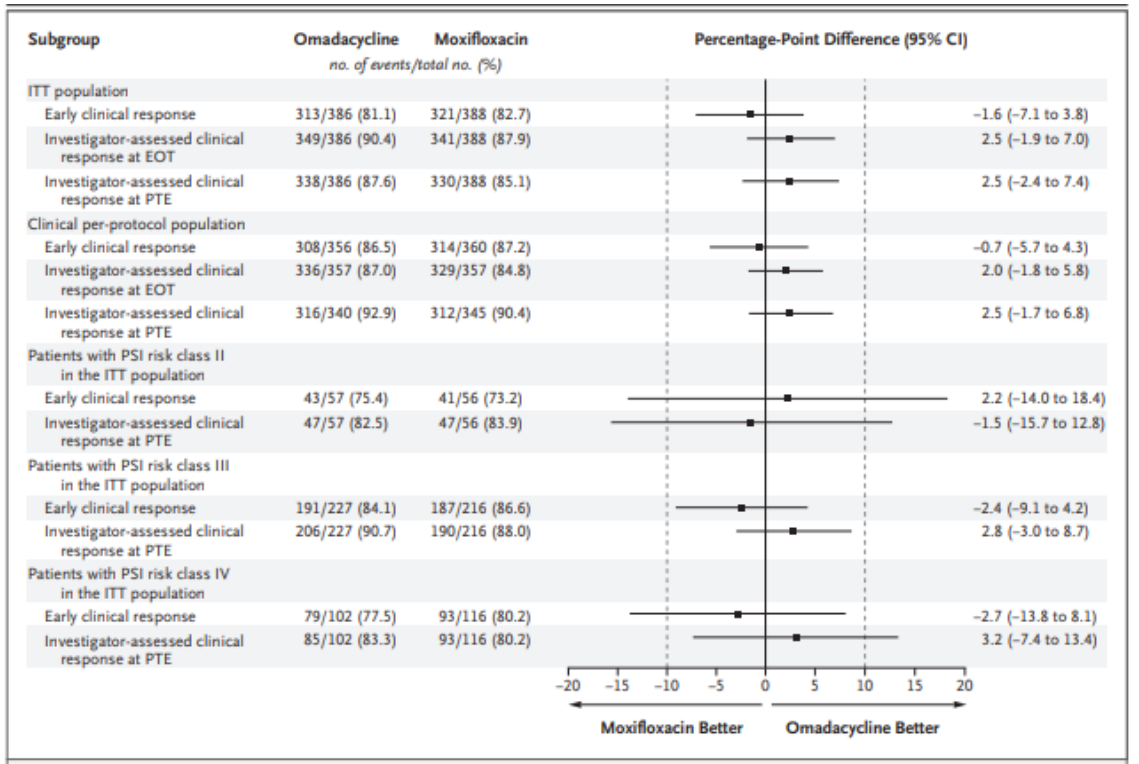
Omadacycline

Omadacycline was noninferior to moxifloxacin for early clinical response

Treatment related AE occurred in 41.1% of patients in the Omdacycline group and 48.5% of patients in the moxifloxacin group

Twelve deaths (8 in the omadacycline group and 4 in the moxifloxacin group) occurred during the trial.



Subgroup	Omadacycline	Moxifloxacin	Percentage-Point Difference (95% CI)
	no. of events/total no. (%)		
ITT population			
Early clinical response	313/386 (81.1)	321/388 (82.7)	−1.6 (−7.1 to 3.8)
Investigator-assessed clinical response at EOT	349/386 (90.4)	341/388 (87.9)	2.5 (−1.9 to 7.0)
Investigator-assessed clinical response at PTE	338/386 (87.6)	330/388 (85.1)	2.5 (−2.4 to 7.4)
Clinical per-protocol population			
Early clinical response	308/356 (86.5)	314/360 (87.2)	−0.7 (−5.7 to 4.3)
Investigator-assessed clinical response at EOT	336/357 (87.0)	329/357 (84.8)	2.0 (−1.8 to 5.8)
Investigator-assessed clinical response at PTE	316/340 (92.9)	312/345 (90.4)	2.5 (−1.7 to 6.8)
Patients with PSI risk class II in the ITT population			
Early clinical response	43/57 (75.4)	41/56 (73.2)	2.2 (−14.0 to 18.4)
Investigator-assessed clinical response at PTE	47/57 (82.5)	47/56 (83.9)	−1.5 (−15.7 to 12.8)
Patients with PSI risk class III in the ITT population			
Early clinical response	191/227 (84.1)	187/216 (86.6)	−2.4 (−9.1 to 4.2)
Investigator-assessed clinical response at PTE	206/227 (90.7)	190/216 (88.0)	2.8 (−3.0 to 8.7)
Patients with PSI risk class IV in the ITT population			
Early clinical response	79/102 (77.5)	93/116 (80.2)	−2.7 (−13.8 to 8.1)
Investigator-assessed clinical response at PTE	85/102 (83.3)	93/116 (80.2)	3.2 (−7.4 to 13.4)

Figure 2. Forest Plot of Primary and Secondary End Points.

The 95% confidence intervals are based on the Miettinen and Nurminen method without stratification.[38] Scores on the Pneumonia Severity Index (PSI) are used to place patients with pneumonia into risk classes that range from I to V, with higher risk classes indicating a greater risk of death (additional details are provided in the protocol); in this trial, only patients in risk class II (PSI score, 51 to 70), III (71 to 90), or IV (91 to 130) were eligible for participation. EOT denotes end of treatment, ITT intention to treat, and PTE post-treatment evaluation.

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Omadacycline for Community-Acquired Bacterial Pneumonia

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Omadacycline

Omadacycline administered in combination with other antimicrobials was relatively safe over a median duration of eight months.

- Adverse events that were directly attributed to omadacycline were reported in 29% of patients

Promising effectiveness of omadacycline-containing regimens in patients with a high prevalence of macrolide resistance.

- 23% of those with refractory pulmonary disease had two consecutive negative cultures with no subsequent positive cultures

Characteristic	No. (%)
Duration of treatment, mo	
Median	8
Range	0.25–33
Interquartile range	4–15
Dose of omadacycline	
150 mg daily	4 (3.4)
300 mg daily	112 (95.7)
Unspecified	1 (<1)
Rationale for use of omadacycline[a]	
Initial therapy	13 (11.1)
Transition from intravenous therapy	54 (46.2)
Addition to regimen for treatment of refractory disease	37 (31.6)
Intolerance to other NTM therapy	28 (23.9)
Patients who discontinued therapy during study period	60 (51.3)
Reason for discontinuation, No. (% of total treated, N = 117)	
Completion of planned therapy	20 (17.1)
Adverse event or intolerance	23 (19.7)
Cost	7 (6.0)
Death (not related to NTM infection or treatment)	4 (3.4)
Other[b]	6 (5.1)

Open Forum Infectious Diseases

MAJOR ARTICLE

Long-term Safety and Tolerability of Omadacycline for the Treatment of *Mycobacterium abscessus* Infections

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The Classics

- Quinolones
  - Can still be the right drug for the job despite risks
- TMP/SMX
  - Dosing is key
- Linezolid
- First generation cephalosporins
  - Dosing is key, emerging data

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Sulopenem: Hot off the Presses

- Oral carbapenem approved in October 2024 for treatment of uncomplicated cystitis in adult women
- Data based on two non-inferiority trials. Studies for complicated UTI and intrabdominal infections did not meet level of evidence needed for approval
- Oral formulation packaged with probenecid, which may increase side effects

Overall Response at Test of Cure by Step-Down Category: Microbiologic Modified Intent-to-Treat Population

Outcome	Sulopenem, n/N (%)	Ertapenem, n/N (%)	Difference, % (95% Confidence Interval)
All patients			
âPrimary end point: overall success (test of cure)	301/444 (67.8)	325/440 (73.9)	−6.1 (−12.0 to −.1)
âReason for failure: asymptomatic bacteriuria	93 (20.9)	59 (13.4)	
Patients with ciprofloxacin-susceptible isolates by treatment regimen			
	Sulopenem IV/oral sulopenem, n/N (%)	Ertapenem IV/oral ciprofloxacin, n/N (%)	
âOverall success	168/248 (67.7)	186/215 (86.5)	−18.8 (−26.1 to −11.0)
âReason for failure: asymptomatic bacteriuria	54 (21.8)	10 (4.7)	

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Summary

- **Long-acting infusion antibiotics and oral stepdown are excellent options to avoid the complications of OPAT in the right patient population**
- **Dalbavancin has a high level of evidence supporting its use in significant staph infections**
- **Consider patient and drug level factors which could influence the efficacy of this approach**

Questions?

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Thank you

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