U.S. Department of Veterans Affairs

Efficacy and Safety of Dalbavancin and Oritavancin in the Treatment of Gram-Positive Infections

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DISCLAIMER

- This material is the result of work supported with resources and the use of facilities at the VA St. Louis Health Care System.

- The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

- This study was approved by the Institutional Review Board (IRB) at the VA St. Louis Health Care System

BACKGROUND

- Lipoglycopeptides (Dalbavancin, Oritavancin)
  - Increased potency against multi-drug resistant pathogens
  - Treat serious infections with just one or two doses
    - Increased compliance, ease of administration, decreased cost
  - FDA approved for acute bacterial skin and skin structure infections (ABSSSI) only
    - Often used in osteomyelitis (OM) and bloodstream infections (BSI)
  - Recent trials show efficacy and safety in OM and BSI

Brade K et al. *Infect Dis Ther*. 2016(5)1:15.
Sievert D et al. *Infect Control Hosp Epidemiol.* 2013;34:1-14.
Corey G et al. *N Engl J Med.* 2014;370:2180-90.
Rappo U et al. *Open Forum Infect Dis*. 2019;6(1):1-8.
Raad I et al. *Clin Infect Dis.* 2005;40:374-80.

OBJECTIVE

- To describe the safety and efficacy of lipoglycopeptides for ABSSSI, OM, and BSI

Exploratory Endpoints

- To compare the efficacy of lipoglycopeptides to a local historical control for specific infections
- Explore potential predictors of success/failure of treatment
- To compare the safety between single and two-dose regimens

CLINICAL SUCCESS DEFINITION

ABSSSI

- No administration of antibiotics within 4 weeks
- No hospital admission for ABSSSI of same site within 4 weeks

OM

- No administration of antibiotics within 6 months
- No unplanned surgery for OM of same site within 6 months

- Safety– adverse drug reactions within 4 weeks
  - Injection site reactions, nausea, vomiting, diarrhea, headache, rash

METHODS

- Collect and describe outcomes of use of lipoglycopeptide
- Clinical success compared to historical controls
- Evaluate Potential Predictors
  - Empiric versus definitive treatment
  - Intravenous drug users versus non-intravenous drug users
  - Monotherapy versus combination therapy
  - MRSA versus non-MRSA infections
  - Dalbavancin versus Oritavancin
  - ABSSSI versus BSI versus OM

STATISTICAL ANALYSIS

- Baseline Characteristics
  - Categorical: Chi-square or Fisher's exact
  - Continuous: independent T-test or Wilcoxon-ranked sum
- Descriptive Analysis: descriptive statistics, chi-square, t-test
- Exploratory Analysis: chi square, multivariate regression
- Pilot study: no power calculation

INCLUSION CRITERIA

- Patients aged ≥ 18 to ≤ 89 years old
- Receipt of dalbavancin or oritavancin
- Active infection (ABSSSI, OM, or BSI)
- ABSSSI
  - Documented as soft tissue infection not involving bone; may require surgery; 1 dose appropriate
  - At least 2 signs/symptoms: drainage/discharge, erythema, fluctuance, localized warmth, pain or tenderness to palpation, swelling
- OM (at least one of the following)
  - X-ray, CT, or MRI specifying OM
  - Followed by ID physician and documented as OM
- BSI
  - Positive blood cultures with growth of gram-positive organism within 96 hours of administration of study drug

EXCLUSION CRITERIA

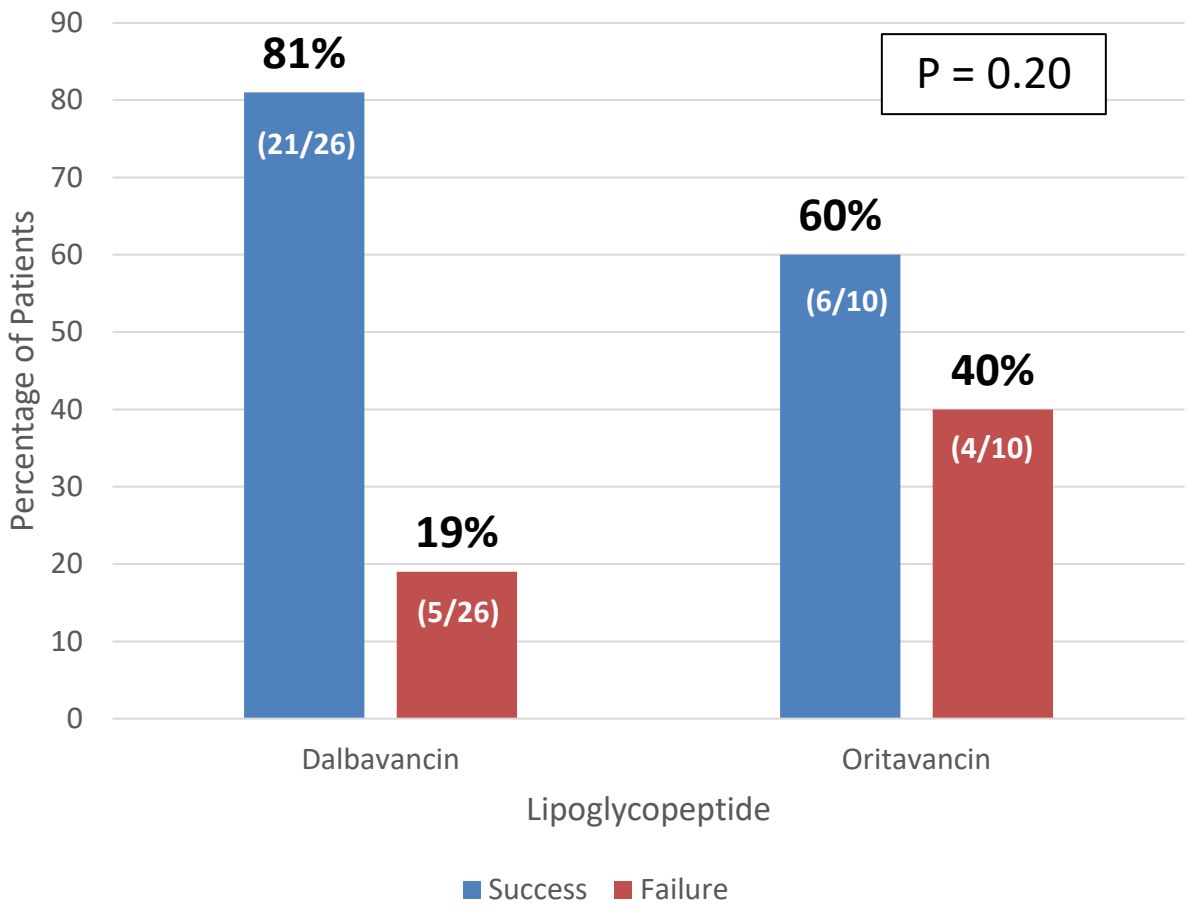
- ABSSSI, BSI
  - ≥ 72 hours of any antibiotic before lipoglycopeptide
- OM
  - ≥ 7 days of any antibiotic before lipoglycopeptide
- ≥ 48 hours of additional intravenous antibiotics after administration of dalbavancin or oritavancin

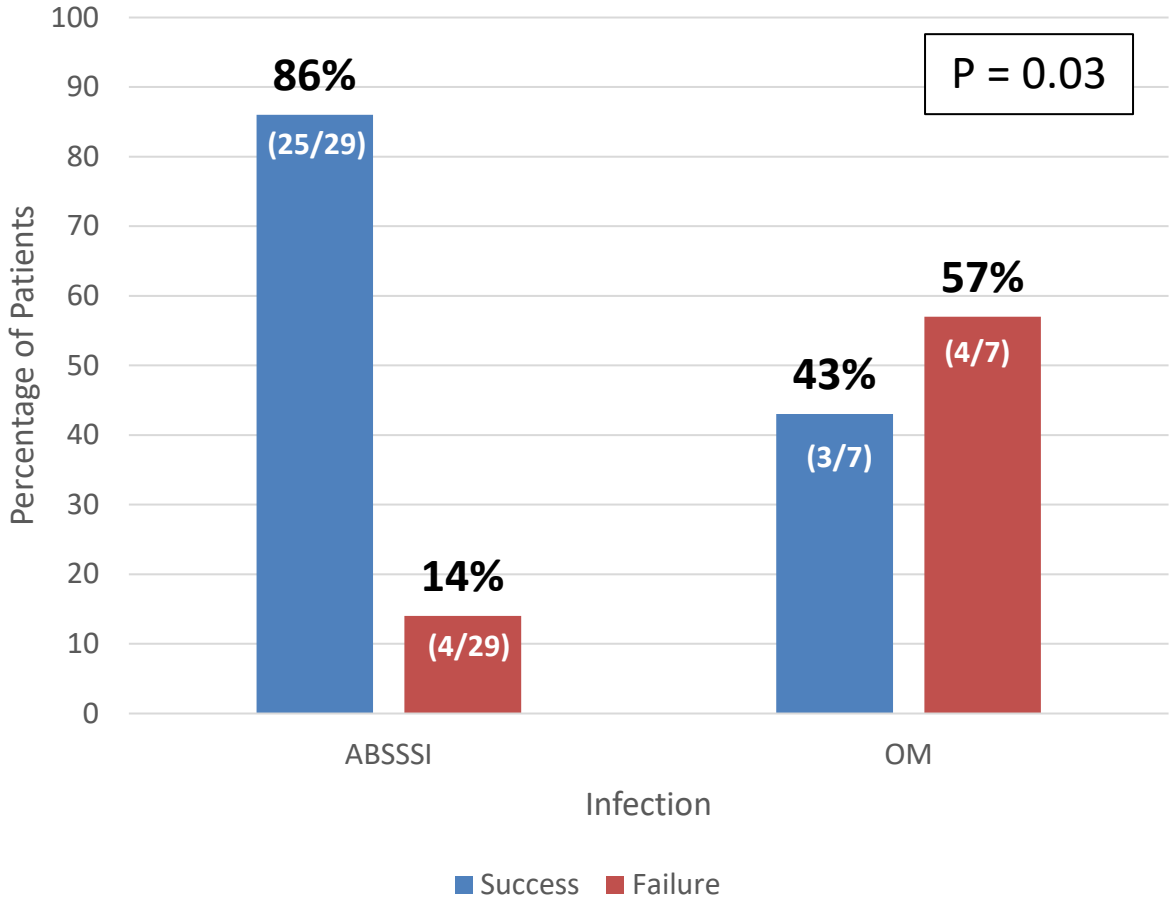
Baseline Characteristic	Overall (N = 36)	Dalbavancin (N = 26)	Oritavancin (N = 10)	P-value
Age (avg years ± SD)	65 ± 9.8	66 ± 10.2	63 ± 8.2	0.33
Caucasian—no. (%)	26 (72%)	18 (69%)	8 (80%)	0.69
CrCl at initiation—mL/min	84 ± 34	81 ± 35	91 ± 30	0.43
WBC at initiation—10^3/uL	9.4 ± 3.6	9.2 ± 3.4	9.8 ± 4	0.70
Empiric treatment—no. (%)	20 (56%)	17 (65%)	10 (100%)	**0.04**
Received abx prior	25/36 (69%)	16/26 (61.5%)	9/10 (90%)	0.127
Duration of abx prior, if received (avg days ± SD)	2.6 ± 1.2	2.5 ± 0.7	2.8 ± 1.5	0.60
Received abx after	10/36 (28%)	6/26 (23%)	4/40 (40%)	0.413
Duration of abx after, if received (avg days ± SD)	28 ± 14	28 ± 13	27 ± 15	0.93
ABSSSI—no. (%)	29 (81%)	22 (85%)	7 (70%)	0.37
OM—no. (%)	7 (19%)	4 (15%)	3 (30%)	

Baseline Characteristic	Overall (N = 36)	ABSSSI (N = 29)	OM (N = 7)	P-value
Age—yr	65 ± 9.8	65 ± 9.6	69 ± 10	0.36
Caucasian—no. (%)	26 (72%)	21 (72%)	5 (71%)	0.18
CrCl at initiation—mL/min	84 ± 34	86 ± 36	76 ± 26	0.50
WBC at initiation—$10^3/\mu L$	9.4 ± 3.6	9.4 ± 3.7	9.4 ± 3.2	0.99
Empiric treatment—no. (%)	20 (56%)	19 (65%)	1 (14%)	**0.03**
Received abx prior	25/36 (69%)	18/29 (62.1%)	7/7 (100%)	0.076
Duration of abx prior, if received (avg days ± SD)	2.6 ± 1.2	2.2 ± 0.7	3.6 ± 2	0.19
Received abx after	10/36 (28%)	4/29 (14%)	6/7 (85.7%)	**0.001**
Duration of abx after, if received (avg days ± SD)	28 ± 14	13 ± 1.7	36 ± 10.2	**0.001**
Dalbavancin—no. (%)	26 (72%)	22 (76%)	4 (57%)	0.37
Oritavancin—no. (%)	10 (28%)	7 (24%)	3 (43%)	

OVERALL RESULTS

Overall, clinical success occurred in 77.7% (28/36) of the lipoglycopeptide cohort, regardless of agent or infection





HISTORICAL CONTROL—ABSSSI

- **Primary Outcome:** clinical failure
  - ED visit, clinic visit, or admission for ABSSSI within 14 days of treatment completion
  - IV antibiotic administration for ABSSSI within 14 days of treatment completion
  - Extension or switch to different PO antibiotic for ABSSSI for any reason within 14 days of treatment completion

Inclusion Criteria

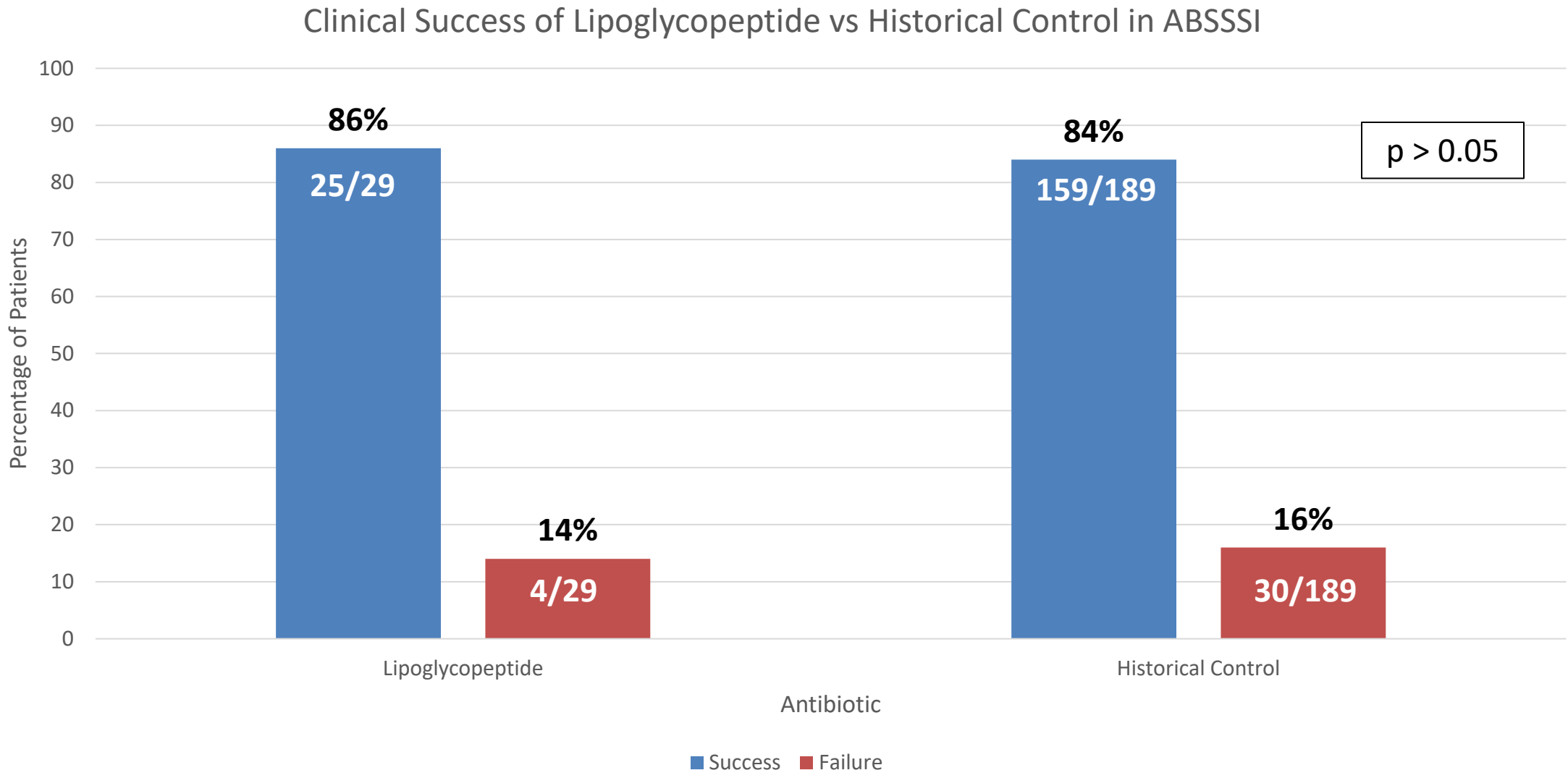
- ICD-9 or 10 admission code for skin infection
- Received outpatient Rx for Linezolid or Bactrim for ≥ 5 days at time of discharge

Exclusion Criteria

- Directly discharged from ED
- Receipt of concomitant antibiotics with Linezolid or Bactrim

Tan, et al. OFID, S574, 2018

RESULTS—ABSSSI



HISTORICAL CONTROL—OM

- **Primary Outcome:** clinical failure
  - Receipt of antibiotics for infection of same anatomical site within 6 months of discontinuation
  - Unplanned surgical intervention or infection of same anatomical site within 6 months of discontinuation

Inclusion Criteria

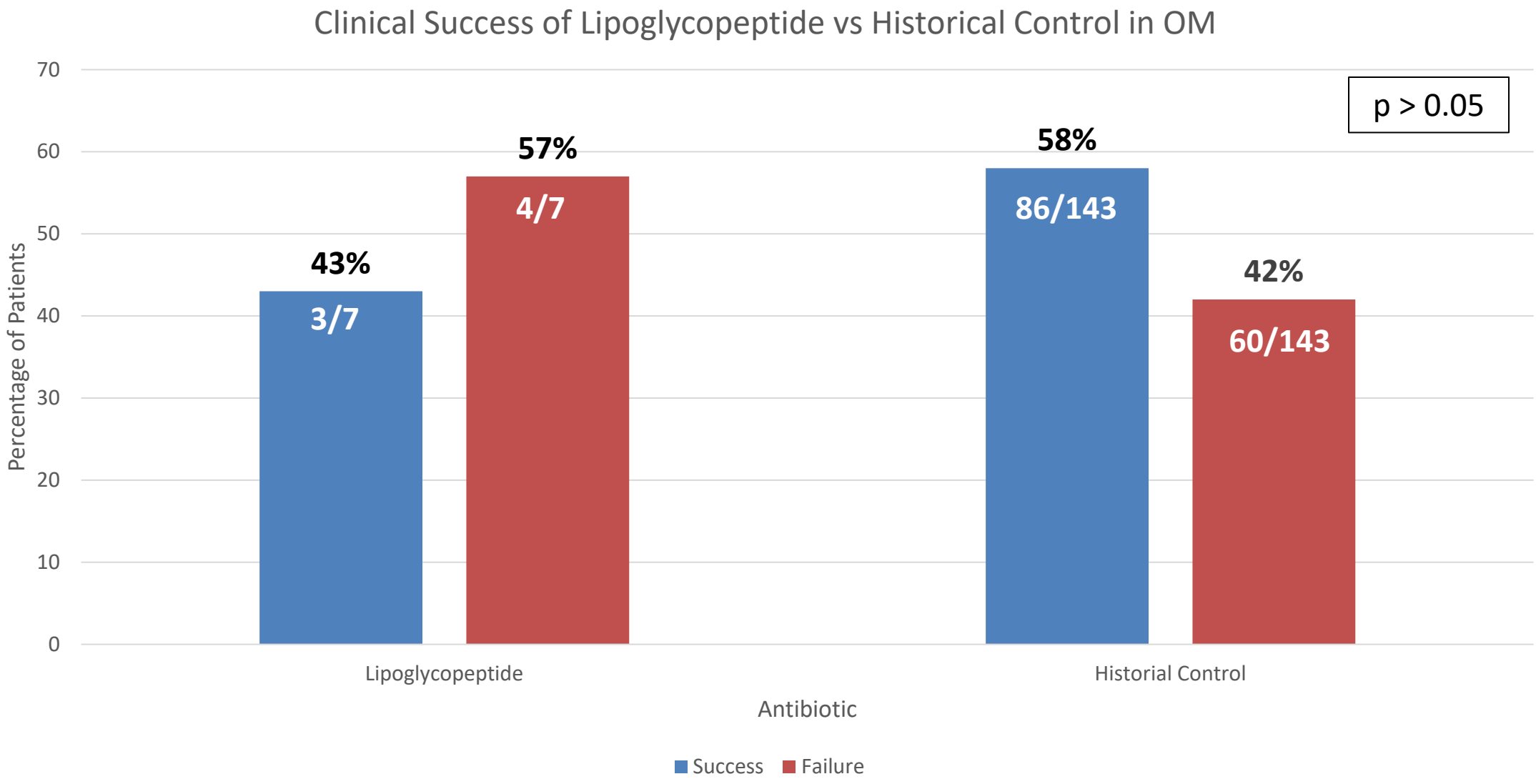
- Diagnosed with OM by imaging, tissue pathology report, or ID note confirming diagnosis
- Receipt of ≥ 2 weeks IV antibiotics at home or SNF
- Receipt of ≥ 4 weeks of PO antibiotics for OM (not including suppression)

Exclusion Criteria

- Diagnosis of:
  - Rheumatoid arthritis
  - Temporal arteritis
  - Sickle cell disease
  - Polycythemia
  - Lupus
  - Multiple Myeloma
  - Cancer with or without malignancy
- Steroid use

Pearson D, et al. OFID, S519, 2019

RESULTS—OM


Clinical Success of Lipoglycopeptide vs Historical Control in OM
p > 0.05
70
60
50
40
30
20
10
0
Percentage of Patients
43%
3/7
57%
4/7
58%
86/143
42%
60/143
Lipoglycopeptide
Historial Control
Antibiotic
Success
Failure

RESULTS—UNIVARIATE ANALYSIS

Risk Factors	Clinical Success (N=28)	Clinical Failure (N=8)	P-value
Empiric treatment	16 (57%)	4 (50%)	1.0
IVDA	2 (7%)	0 (0%)	1.0
Monotherapy	21 (75%)	5 (63%)	0.39
MRSA	6 (21%)	1 (13%)	1.0
Dalbavancin	22 (79%)	4 (50%)	**0.18**
ABSSSI	25 (89%)	4 (50%)	**0.03**

RESULTS—MULTIVARIATE REGRESSION

Multivariate analysis for risk factors associated with clinical success

Risk Factors	OR (95% CI)	P-value
Dalbavancin	0.313 (0.051-1.917)	0.21
ABSSSI	0.132 (0.020-0.786)	0.04

ABSSSI is associated with 87% reduction in risk of treatment failure versus osteomyelitis

RESULTS—SAFETY

Adverse Drug Reaction	Single Dose Regimen (N=32)	Two Dose Regimen (N=4)
Injection-site reaction	0	0
Nausea	2	0
Vomiting	2	0
Diarrhea	0	1
Headache	1	0
Total of unique patients with ADRs	3	1

DISCUSSION

- Dalbavancin was the most common lipoglycopeptide used and ABSSSI was the most common treated infection
- Clinical success was significantly higher in ABSSSI vs OM and slightly higher with dalbavancin, although not significant
- Lipoglycopeptide in ABSSSI associated with 86% clinical success rate
  - Boucher et al: 90.7% clinical success rate with dalbavancin
  - Corey et al: 79.6% clinical success rate with dalbavancin
- Rappo et al: 97% success rate with dalbavancin in OM

Boucher H, et al. *N Engl J Med*. 2014;370(23):2169-2179.
Corey G,e t al. *N Engl J Med.* 2014;370(23):2180-2190.
Rappo U, et al. *Open Forum Infect Dis*. 2018;6(1):ofy331.

DISCUSSION

Strengths

- Exclusion of prolonged duration of antibiotics prior to lipoglycopeptide
- Multiple types of infections
- 5-year time period
- Historical control included patients from same medical center
- Limited data on lipoglycopeptide efficacy

Limitations

- Retrospective, single-center
- Small sample size
- Variable durations of antibiotics prior to lipoglycopeptide
- Use of historical control instead of comparator group
- Difference in definitions of outcomes in historical control

CONCLUSIONS

- Clinical success occurred in 77.7% (28/36) of the lipoglycopeptide cohort, regardless of agent or infection
  - Success rates were higher for ABSSSI vs OM
- Clinical success of lipoglycopeptide treatment in ABSSSI and OM was comparable to historical controls
- No difference in safety between single- and 2-dose regimens

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