Dalbavancin (Dalvance®)

National Drug Monograph

April 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

FDA Approval Information

Description/Mechanism of Action	Dalbavancin is lipoglycopeptide antibacterial drug that interrupts cell wall synthesis by binding to the terminal D-alanyl-D-alanine of cell wall peptidoglycan and preventing cross-linking[1]
Indication(s) Under Review in this document (may include off label)	Treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus anginosus* group (including *S. anginosus, S. intermedius, S. constellatus*)[1]
Dosage Form(s) Under Review	Sterile powder for injection; 500 mg single-use clear glass vials
REMS	☐ REMS ☐ No REMS
Pregnancy Rating	Category C

Executive Summary

Efficacy	• The FDA approval of dalbavancin was based on two phase 3 trials (DISCOVER 1 and DISCOVER 2) which compared dalbavancin to vancomycin (with optional switch to oral linezolid) in patients with ABSSSI known or suspected to be caused by Gram-positive bacteria.[2] • The primary efficacy endpoint was early clinical response at 48-72 hours. The definition of early clinical response was cessation of spread of lesion and the absence of fever at 48 to 72 hours. • In a pooled analysis, 525/659 (79.7%) of dalbavancin patients exhibited an early clinical response compared to 521/653 (79.3%) of patients on comparator therapy.[2]
Safety	• The most common adverse effects (≧2%) include nausea, headache, diarrhea, constipation, vomiting, rash, and pruritis.[1,2] • The warnings and precautions state that in clinical trials more patients receiving dalbavancin had ALT elevations greater than 3 times the upper limit of normal (ULN) than patients treated with comparator therapy.[1] • Additional warnings and precautions also caution use in patients with a known hypersensitivity reaction to dalbavancin or other glycopeptide antibiotics. In order to minimize the risk of infusion-related reactions, ie: "Red-Man Syndrome", dalbavancin should be administered via intravenous infusion over 30 minutes.[1]
Potential Impact	• The most recent IDSA guidelines for the treatment of skin and soft tissue infections were updated in June 2014, approximately one month after the FDA approval of dalbavancin. These guidelines recommend vancomycin, daptomycin, linezolid, televancin, or ceftaroline as empiric therapy for treatment of ABSSSIs in addition to incision and drainage.[3] • The results of DISCOVER-1 and DISCOVER-2 demonstrated that dalbavancin is as effective as vancomycin/linezolid for the treatment of ABSSSI caused by Gram-positive bacteria, including infections due to MRSA.[2] • Dalbavancin is indicated for the treatment of ABSSSI. It has an extended half-life which allows for administration in two weekly doses (on Day 1 and Day 8) over a 30 minute infusion.

Background

Purpose for review

The purpose of this review is to evaluate the efficacy and safety of dalbavancin

Issues to be determined:

- ✓ Evidence of need
- ✓ Does dalbavancin offer advantages over currently available VANF antimicrobial agents?
- ✓ What safety issues need to be considered?

Other IV MRSA therapeutic options

Formulary Alternatives	Other Considerations in Adults [3,4,5,6]
Ceftaroline	• Availability: IV • Limited experience with other MRSA infections besides skin and skin structure infections • Pregnancy category B
Daptomycin	• Availability: IV • Possible cross-resistance with vancomycin • Associated with myopathies and CPK monitoring is recommended • Pregnancy category B
Linezolid	• Availability: IV and PO • Long term use limited by hematologic toxicity, peripheral and optic neuropathy and lactic acidosis. • Reversible inhibitor of monoamine oxidase with possible drug interaction with SSRIs. • Pregnancy category C
Vancomycin	• Availability: IV • Requires monitoring of levels and has been shown to kill *Staphylococcus* more slowly than β-lactams • Associated with nephrotoxicity and Redman syndrome • Pregnancy category C

Please refer to PBM Recommendations for Newer Gram-Positive Agents for more details including information on tedizolid, telavancin, and tigecycline.

Efficacy (FDA Approved Indications)

Literature Search Summary

A literature search was performed on PubMed/Medline (through May 2015) using the search terms dalbavancin and Dalvance. The search was limited to studies performed in humans and published in the English language. A total of five Phase 3 randomized controlled trials published in peer-reviewed journals were identified. Included are the two pivotal Phase 3 randomized controlled trials that led FDA approval of dalbavancin.

Review of Efficacy

The FDA approval of dalbavancin was based on two pivotal Phase 3 randomized, double-blind, double-dummy, non-inferiority, multicenter, international clinical trials (DISCOVER 1 and DISCOVER 2).[2] DISCOVER 1 and DISCOVER 2 were identical trials comparing two weekly doses of dalbavancin (on Day 1 and Day 8) with vancomycin (with optional switch to oral linezolid) in patients with ABSSSI known or suspected to be caused by Gram-positive bacteria. ABSSSI was defined as any of the following[2]:

- Cellulitis: Characterized by erythema, edema, and/or induration
- Major abscess: Collection of pus requiring incision and drainage and a margin of erythema ≥5 cm in all directions from the border of induration or edema

- Wound infection: Surgical site or traumatic wound infection that occurred within 30 days of surgery or trauma, and required purulent drainage and a margin of erythema that was ≥5 cm in at least one direction from the edge ofthe wound

Patients were assigned a treatment group in a 1:1 ratio to receive dalbavancin 1000 mg IV on Day 1 followed by 500 mg IV on Day 8 or vancomycin 1000 mg or 15 mg/kg every 12 hours for at least three days, up to 10 to 14 days. Patients in the vancomycin group had the option to change to oral linezolid 600 mg every 12 hours to complete the course of therapy. All doses of dalbavancin and vancomycin were renally adjusted, when necessary. In addition, clinicians at the individual study sites decided whether to use fixed dose or weight based vancomycin dosing, though no goal trough concentration or results of therapeutic drug monitoring were reported.[2]

The primary efficacy endpoint was early clinical response (cessation of spread of lesion and the absence of fever at 48 to 72 hours). A key secondary endpoint was a ≥20% reduction in lesion area from baseline. Additional efficacy endpoints included clinical status at the end of therapy and investigator assessment of outcome.[2] These were defined as follows:

- Clinical status at the end of therapy
  - Success – lesion size decreased from baseline, temperature ≤37.6 C, fluctuance and localized heat/warmth were absent, tenderness to palpation and swelling/induration were no worse than mild. For patients with a wound infection, the purulent drainage was to be improved and no worse than mild Failure – criteria for
  - success were not met or patient received a new, non-study antibacterial treatment for ABSSSI, died during the study period, required an unplanned surgical intervention within 72 hours of starting therapy, or received study therapy for ABSSSI beyond the specified protocol treatment period
- Investigator assessment of outcome
  - Patients were assessed at baseline, every 12 hours through day 4, at day 8, at the end of therapy (day 14-15), for short-term follow-up (day 28), and for long-term follow-up (day 70)

Inclusion and exclusion criteria are listed in Table A. In both trials, demographic and baseline characteristics were similar between the two treatment groups (refer to Table B). Both trials met their primary objectives of demonstrating dalbavancin non-inferiority to comparator therapy based on early clinical response at 48-72 hours using a 10% non-inferiority margin.[2]

Table A. Key Inclusion/Exclusion Criteria[2]

Inclusion Criteria	Exclusion Criteria
Adults with a diagnosis of ABSSSI (cellulitis, major abscess, or wound infection) believed to require at least 3 days of IV therapy with one or more of the following systemic signs of infection - Elevated body temperature (>38°C) - WBC > 12,000 cells/m^3 - >10% bands on differential count - Erythema with at least two of the following: purulent drainage or discharge, fluctuance, heat, tenderness, swelling or induration	Receipt of antibiotic therapy within 14 days before randomization occurred

Table B. Baseline Characteristics[2,7]

	DISCOVER 1		**DISCOVER 2**	
	Dalbavancin n=288	**Vancomycin/Linezolid n=285**	**Dalbavancin n=371**	**Vancomycin/Linezolid n=368**
Age (mean)	48.8	48.9	49.1	51.4
Male sex	170 (59.0%)	173 (60.7%)	328 (88.4%)	320 (87.0%)
Region of Enrollment				
US or Canada	123 (42.7%)	121 (42.5%)	115 (31.0%)	114 (31.0%)
Europe, Asia, or South Africa	165 (57.3%)	164 (57.5%)	256 (69.0%)	254 (69.0%)
Race				
White	264 (91.7%)	259 (90.9%)	328 (88.4%)	320 (87.0%)
Black	16 (5.6%)	19 (6.7%)	13 (3.5%)	17 (4.6%)
Other	8 (2.8%)	7 (2.5%)	30 (8.1%)	31 (8.4%)

Infection type				
Cellulitis	156 (54.2%)	147 (51.6%)	198 (53.4%)	202 (54.9%)
Major abscess	72 (25.0%)	86 (30.2%)	90 (24.3%)	87 (23.6%)
Wound infection	60 (20.8%)	52 (18.2%)	82 (22.1%)	79 (21.5%)
Relevant Characteristics				
Median lesion size (cm^2)	333	368	314	362
Temperature ≥38°C	243 (85.6%)	242 (85.2%)	306 (83.8%)	310 (84.9%)
WBC >12,000/mm^3	98 (37.8%)	104 (40.9%)	149 (40.5%)	146 (39.8%)
White cell bands >10%	63 (26.5%)	66 (27.0%)	48 (19.9%)	42 (17.9%)
SIRS	175 (61.6%)	175 (61.6%)	157 (42.7%)	161 (43.8%)
Bacteremia	8 (2.8%)	6 (2.1%)	20 (5.4%)	11 (3.0%)

SIRS: Systemic Inflammatory Response Syndrome

Table C. Primary and Key Secondary Endpoints[2]

Endpoint	Dalbavancin	Vancomycin/Linezolid	Absolute Difference (95% CI)
Primary Efficacy Endpoint: Early clinical response at 48-72 hours (performed in the ITT population)			
DISCOVER 1	240/288 (83.3%)	233/285 (81.8%)	1.5 (-4.6 to 7.9)
DISCOVER 2	285/371 (76.8%)	288/368 (78.3%)	-1.5 (-7.4 to 4.6)
Both trials	525/659 (79.7%)	521/653 (79.3%)	-0.1 (-4.5 to 4.2)
Key Secondary Efficacy Endpoint: ≥ 20% reduction in lesion area from baseline at 48-72 hours (performed in the ITT population)			
DISCOVER 1	259/288 (89.9%)	259/285 (90.9%)	-1.0 (-5.7 to 4.0)
DISCOVER 2	325/371 (87.6%)	316/368 (85.9%)	1.7 (-3.2 to 6.7)
Both trials	584/659 (88.6%)	575/653 (88.1%)	0.6 (-2.9 to 4.1)
Secondary Efficacy Endpoint: Clinical status at the end of therapy (performed in the clinical per-protocol population)			
DISCOVER 1	214/246 (87.0%)	222/243 (91.4%)	-4.4 (-9.6 to 1.6)
DISCOVER 2	303/324 (93.5%)	280/302 (92.7%)	0.8 (-3.3 to 4.9)
Both trials	517/570 (90.7%)	502/545 (92.1%)	-1.5 (-4.8 to 1.9)
Secondary Efficacy Endpoint: Investigator's assessment of outcome (performed in the clinical per-protocol population)			
DISCOVER 1	233/246 (94.7%)	237/243 (97.5%)	-2.8 (-6.7 to 0.7)
DISCOVER 2	314/324 (96.9%)	290/302 (96.0%)	0.9 (-2.2 to 4.1)
Both trials	547/570 (96.0%)	527/545 (96.7%)	-0.7 (-3.0 to 1.5)

Overall quality of evidence: High (Refer to Appendix A); please note that all trials were funded by manufacturer.

Table D. Primary Efficacy Endpoint and Key Secondary Efficacy Endpoint According to Baseline Pathogen[1]

	Early Clinical Response		≥20% Reduction in Lesion Size	
Pathogen	Dalbavancin	Vancomycin/Linezolid	Dalbavancin	Vancomycin/Linezolid
Staph. aureus	206/257 (80.2%)	219/256 (85.5%)	239/257 (93.0%)	232/256 (90.6%)
MSSA	134/167 (80.2%)	163/189 (86.2%)	156/167 (93.4%)	173/189 (91.5%)
MRSA	72/90 (80.0%)	56/67 (83.6%)	83/90 (92.2%)	59/67 (88.1%)
Strep. agalactiae	6/12 (50.0%)	11/14 (78.6%)	10/12 (83.3%)	10/14 (71.4%)
Strep. pyogenes	28/37 (75.7%)	24/36 (66.7%)	32/37 (86.5%)	27/36 (75.0%)
Strep. anginosus group	18/22 (81.8%)	23/25 (92.0%)	21/22 (95.5%)	25/25 (100%)

Summary of efficacy

- In a pooled analysis, 525/659 (79.7%) of dalbavancin patients exhibited an early clinical response compared to 521/653 (79.3%) of patients on comparator therapy.

- For patients infected with *S. aureus*, early clinical response was seen with 80.2% of patients receiving dalbavancin therapy and 85.5% of patients receiving comparator therapy.
- The DISCOVER trials demonstrated that the efficacy of dalbavancin was not inferior to vancomycin/linezolid therapy for the treatment of ABSSSIs.

Potential Off-Label Use

- Single dose dalbavancin or single dose dalbavancin followed by alternative oral antibacterial therapy
- Treatment of Gram-positive infections other than ABSSSIs[3]
- A Phase 3 trial sponsored by the manufacturer comparing single dose dalbavancin to two dose dalbavancin for the treatment of ABSSSIs is ongoing[8]
- A Phase 3 trial sponsored by the manufacturer comparing single dose dalbavancin to twice daily linezolid for the treatment of community acquired bacterial pneumonia is planned but not yet recruiting participants[9]
- A Phase 3 trial sponsored by the manufacture comparing dalbavancin to comparator therapy for pediatric osteomyelitis is planned but not yet recruiting participants[10]

Safety

(for more detailed information refer to the product package insert)

	Comments
Boxed Warning	▪ None
Contraindications	▪ Contraindicated in patients with known hypersensitivity to dalbavancin
Warnings/Precautions	▪ **Hypersensitivity reactions:** Serious hypersensitivity (anaphylactic) and skin reactions have been reported in patients treated with dalbavancin. Inquire carefully about previous hypersensitivity reactions to glycopeptides, and due to the possibility of cross-sensitivity, exercise caution in patients with a history of glycopeptide allergy. ▪ **Infusion related reactions:** Rapid intravenous infusions can cause reactions that resemble "Red-Man Syndrome," including flushing of the upper body, urticaria, pruritus, and/or rash. Stopping or slowing the infusion may result in cessation of these reactions. ▪ **Hepatic effects:** In clinical trials, more patients treated with dalbavancin had ALT elevation greater than 3 times the ULN than patients in the comparator arm. ▪ ***Clostridium difficile*-associated diarrhea:** *C. difficile* infection has been reported in users of nearly all systemic antibacterial drugs, including dalbavancin, with severity ranging from mild diarrhea to fatal colitis. ▪ **Development of drug-resistant bacteria:** Dalbavancin use in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug resistant bacteria.

Safety Considerations

The safety of dalbavancin was evaluated in 23 clinical studies; fourteen phase 1 studies, two phase 2 studies and seven phase 3 studies [7,11] The data from 1303 patients included in the phase 3 DISCOVER trials are outlined below. Please note that adverse events emerging during treatment were those with an onset or worsening severity at or after administration of the first dose of the study drug through the long-term follow-up visit (day 70).[2]

- Overall, adverse events were reported in fewer patients treated with dalbavancin than in those treated with comparator therapy in the DISCOVER trials[2].
    - 32.8% (n=214) of patients treated with dalbavancin reported an adverse event as compared to 37.9% (n=247) of patients treated with comparator therapy. The majority of adverse events were classified as mild.[2]
    - Median duration of adverse events were 4.0 days (range 1 to 101) in patients receiving dalbavancin and 3.0 days (range 1 to 86) in patients receiving comparator therapy[2]
    - Mean ($\pm$ SD) durations were 8.7 $\pm$ 12.7 days and 8.7 $\pm$ 12.6 days for dalbavancin and comparator therapy, respectively.[2]
- In the DISCOVER trials, adverse events related to hypersensitivity reactions were similar with dalbavancin and comparator therapy, 6.6% (n=43) compared to 8% (n=52), respectively.[2,11]

- In the dalbavancin group, a single anaphylactoid reaction considered related to the study drug was reported. The infusion was stopped and the patient was administered epinephrine, midazolam, hydrocortisone, famotidine, and two additional antihistamines. Endotracheal intubation was not required and signs/symptoms resolved within 60 minutes.[11]

- Several dalbavancin-treated subjects had significant elevations of liver function tests, more than observed in comparator treated subjects in the DISCOVER trials.[11]
  - Six (0.9%) patients in the dalbavancin arm had ALT elevation of greater than 5 times the upper limit of normal including 3 subjects with ALT > 10x ULN. No subjects in the comparator arm had this degree of ALT elevation.[7,11]
- In the DISCOVER trials, infusion site reactions occurred with similar frequencies in the dalbavancin and comparator arms.[2,11]
  - Infusion site-related reactions were seen in 1.4% (n=9) patients treated with dalbavancin and 1.7% (n=11) patients treated with comparator therapy.[2]
  - No dalbavancin-treated subjects developed redman syndrome as compared to 2 comparator-treated subjects.[11]

Adverse Reactions

Common adverse reactions[1]	• **Incidence >2%**: Nausea, headache, diarrhea, vomiting, rash, pruritis
Serious adverse reactions[2]	• Serious AE occurred in 2.6% (n=17) of patients treated with dalbavancin vs. 4.0% (n=26) of patients treated with comparator therapy in phase 3 trials • Two SAEs were considered related to dalbavancin; cellulitis in a single patient and anaphylactoid reaction in a single patient.
Discontinuations due to adverse reactions[2]	• Discontinuation due to AE occurred 2.1% (n=14) with dalbavancin vs. 2.0% (n=13) with comparator therapy in phase 3 trials
Deaths[2]	• A total of 8 deaths occurred in phase 3 trials; 0.2% (n=1) with dalbavancin and 1.1% (n=7) with comparator therapy. • No deaths were considered related to the study medications
Laboratory abnormalities[2]	• In phase 3 trials, 1.1% (n=9) of patients in the dalbavancin arm had ALT elevation of greater than 3 times the ULN compared to 0.2% (n=1) in the comparator group

Drug Interactions

Drug-Drug Interactions

- Dalbavancin is not a substrate, inhibitor, or inducer of CYP 450 enzymes, therefore, there is minimal potential for drug/drug interactions though no clinical drug/drug interaction studies have been conducted

Risk Evaluation

Sentinel event advisories

- None

Sources: ISMP, FDA, TJC

Look-alike/sound-alike error potentials

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Dalbavancin	None	None	None	Telavancin Oritavancin Dactinomycin Daptomycin Dalfampridine
Dalvance	None	None	None	Diovan Besivance Kepivance

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Other Considerations:

Pharmacokinetics[2,7]

Parameter	Dalbavancin
Cmax	287 mg/L
Clearance	0.0513 L/hour
AUC_{0-24}	3185 mg·hr/L
$T_{1/2}$ (terminal)	346 hours
Protein Binding	93%
Metabolism	No apparent metabolism; hydroxy-dalbavancin is a minor metabolite found in the urine, but not plasma, of healthy subjects
Elimination	Feces (20%) and urine (33% unchanged dalbavancin, 12% hydroxy-dalbavancin)

Microbiology

Surveillance data in the United States have evaluated the MIC_{50} and MIC_{90} of dalbavancin and other agents against Gram-Positive isolates. Data were collected from 29 US medical centers in 9 census regions with a total of 1555 clinically significant Gram-positive isolates.[12]

Table D. In Vitro Activity of Dalbavancin and other Agents Reported in a Surveillance Study

Organism	Drug Name	MIC range (mcg/mL)	MIC_{50} (mcg/mL)	MIC_{90} (mcg/mL)
MSSA (n=514)	dalbavancin	≤0.03 – 0.25	0.06	0.06
	vancomycin	≤0.12 – 2.0	1	1
	linezolid	0.5 – 2.0	1	2
	daptomycin	0.12 – 1	0.25	0.5
MRSA (n=522)	dalbavancin	≤0.03 – 0.12	0.06	0.06
	vancomycin	0.5 – 2.0	1	1
	linezolid	0.5 – 8.0	1	1
	daptomycin	0.12 – 1	0.25	0.5
Coagulase negative staphylococci (n=115)	dalbavancin	≤0.03 – 0.25	≤0.03	0.06
	vancomycin	0.5 – 2.0	1	2
	linezolid	0.25 – 2.0	0.5	1
	daptomycin	≤0.06 – 1	0.25	0.5
Streptococcus pyogenes (n=155)	dalbavancin	≤0.03 – 0.12	≤0.03	≤0.03
	vancomycin	0.25 – 0.5	0.25	0.5
	linezolid	0.25 – 1.0	1	1
	daptomycin	≤0.06 – 0.25	≤0.06	≤0.06
Streptococcus agalactiae (n=153)	dalbavancin	≤0.03 – 0.25	≤0.03	0.12
	vancomycin	0.25 – 1.0	0.5	0.5
	linezolid	0.5 – 2.0	1	1
	daptomycin	0.12 – 0.5	0.25	0.25
Viridans group streptococci (n=40)	dalbavancin	≤0.03 – 0.12	≤0.03	0.06
	vancomycin	0.25 – 1.0	0.5	1
	linezolid	0.25 – 2.0	1	1
	daptomycin	≤0.06 – 0.25	0.25	1
Enterococcus spp. (vancomycin-susceptible) (n=30)	dalbavancin	≤0.03 – 0.12	≤0.03	0.06
	vancomycin	0.5 – 2	1	1
	linezolid	0.5 – 2	1	1
	daptomycin	0.25 – 4	1	2
Enterococcus spp. (VanA resistant) (n=24)	dalbavancin	0.25 – >4	>4	>4
	linezolid	0.5 – 2	1	1
	daptomycin	0.5 – 4	1	2
Enterococcus spp. (VanB resistant) (n=2)	dalbavancin	≤0.03	≤0.03	--
	linezolid	1	1	--
	daptomycin	0.5	0.5 – 1	--

Dosing and Administration[1]

Dalbavancin is administered as a 1000 mg intravenous infusion followed one week later by a 500 mg intravenous infusion. It should be administered over 30 minutes by intravenous infusion. Do not reconstitute, dilute, or co-infuse dalbavancin with saline-based infusion solutions due to the potential for precipitation

Special Populations (Adults)

	Comments
Elderly	• No dose adjustment is recommended
Pregnancy	• Category C; There have been no adequate and well-controlled studies with dalbavancin in pregnant women, therefore dalbavancin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus
Lactation	• No data identified; it is not known whether dalbavancin or its • metabolite are excreted in human milk
Renal Impairment	• CrCl <30: 750 mg once followed 7 days later by 375 mg • Patients receiving hemodialysis: No dosage adjustment is recommended
Hepatic Impairment	• Child-Pugh Class A: No dose adjustment is recommended • Child Pugh Class B/C: No data identified
Pharmacogenetics/genomics	• No data identified

Projected Place in Therapy

- The CDC estimates that MRSA caused 80,461 invasive infections and 11,285 deaths in 2011.[13]
- The Infectious Diseases Society of America (IDSA) Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections and IDSA Practice Guidelines for the Management of Patients with Infections caused by MRSA are currently the only two national clinical practice guidelines that discuss MRSA ABSSSIs (dalbavancin's current FDA labeled indication) and both were published prior to the approval of dalbavancin.[3,4]
    - The IDSA Clinical Practice Guidelines for the Management of MRSA Infections recommend clindamycin (A-II), trimethoprim-sulfamethoxazole (A-II), a tetracycline (A-II), and linezolid (A-II) for empirical coverage of community-acquired MRSA in outpatients for the management of skin and soft-tissue infections.[4] IV options for complicated skin and soft-tissue infections requiring hospitalization due to MRSA include vancomycin (A-I), oral or IV linezolid (A-I), daptomycin (A-I), telavancin (A-I), and clindamycin IV or oral (A-III).[4]
    - The IDSA Practice Guidelines for the Diagnosis and Management of Skin and Soft Tissue Infections lists vancomycin, linezolid, clindamycin, daptomycin, ceftaroline, doxycycline/minocycline, and trimethoprim/sulfamethoxazole as antimicrobial treatment options for MRSA.[3]
    - Treatment duration discussed in available guidelines varies from 5 – 14 days depending on guideline and severity of infection.[3,4] Additional agents with FDA labeled indications for MRSA ABSSSIs not included in the guidelines include recently approved tedizolid phosphate and oritavancin.
- Phase 3 clinical studies demonstrated non-inferiority of once-weekly dalbavancin vs twice-daily intravenous vancomycin followed by oral linezolid for the treatment of ABSSSIs.[2] Dalbavancin's prolonged half-life allows for unique dosage regimen that may facilitate parenteral administered therapy for ABSSSI in the emergency department and/or outpatient setting; however, the impact of this prolonged half-life on adverse events needs further surveillance during clinical use.

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Appendix A: GRADEing the Evidence

Designations of Quality

Quality of evidence designation	Description
High	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (2 consistent, higher-quality randomized controlled trials or multiple, consistent observational studies with no significant methodological flaws showing large effects).
Moderate	Evidence is sufficient to determine effects on health outcomes, but the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (1 higher-quality trial with > 100 participants; 2 higher-quality trials with some inconsistency; 2 consistent, lower-quality trials; or multiple, consistent observational studies with no significant methodological flaws showing at least moderate effects) limits the strength of the evidence.
Low	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality studies, important flaws in study design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Please refer to Qaseem A, et al. The development of clinical practice guidelines and guidance statements of the American College of Physicians: Summary of Methods. Ann Intern Med 2010;153:194-199