Ceftaroline, Dalbavancin, Daptomycin, Linezolid, Oritavancin, Quinupristin-dalfopristin, Tedizolid, Telavancin, and Tigecycline
Recommendations for Use
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VHA Pharmacy Benefits Management Services, the Medical Advisory Panel and VISN Pharmacist Executives

The following recommendations are based on current medical evidence and expert opinion from clinicians. The content of the document is dynamic and will be revised as new clinical data becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient situation. The national restriction for antibiotics is that all decisions regarding which agents to carry in these classes will be made at the local or VISN level.

Due to the high specificity of these antibiotics and the potential for the development of resistance, each facility should define a system for approval for use of ceftaroline, dalbavancin, daptomycin, linezolid, oritavancin, quinupristin-dalfopristin, tedizolid, telavancin, and tigecycline to avoid overuse. These antibiotics should only be used in consultation with an Infectious Disease (ID) specialist or following local guidelines approved by local ID experts, except when consultation is not available in a timely manner. Use of these antibiotics should generally be reserved for serious infections for which there are no alternative antimicrobial therapy. Susceptibility should be confirmed prior to use of any of these agents. These newer Gram-positive agents should not be used for empiric therapy of suspected MRSA infections in patients that tolerate vancomycin or who have infections amenable to treatment with oral agents such as TMP/SMX or doxycycline. Of note, dalbavancin and oritavancin have prolonged half-lives that enable unique two-dose and single-dose regimen for treatment of acute bacterial skin and skin structure infections, respectively; this may facilitate administration in the emergency room and/or outpatient clinic. Treatment of MRSA and VRE infections begins with abscess drainage, and with the removal of suspected IV, intra-arterial, or urethral catheters.

Vancomycin-resistant Enterococci (VRE)[a,b,c]

Vancomycin-resistant *Enterococcus faecium*:	**FDA-approved indication:** Linezolid Quinupristin-dalfopristin **Limited to in vitro data and/or clinical experience:** Daptomycin Oritavancin[d] Tedizolid Tigecycline[e]	**Recommendations:** *Selection of specific agent(s) is dependent on multiple factors such as site of infection, co-morbidities, presence of polymicrobial infection.*
Vancomycin-resistant *Enterococcus faecalis*:[f]	**Limited to in vitro data and/or clinical experience:** Daptomycin Linezolid Oritavancin[d] Tedizolid Tigecycline[e]	*Selection of specific agent(s) is dependent on multiple factors such as site of infection, co-morbidities, presence of polymicrobial infection.*

a. For VRE, combination with other agents may be required depending on the site of infection.
b. Vancomycin-resistant enterococci have been associated with asymptomatic bacteriuria and colonization of the urinary tract. Antibiotics are frequently not necessary once the urinary catheter is removed. If antibiotics are deemed necessary, agents such as nitrofurantoin can be used. Tigecycline and tedizolid should be avoided in this setting due to poor urinary concentrations.
c. Telavancin and dalbavancin displays variable in vitro activity against vancomycin-resistant *Enterococcus* spp. It lacks activity against *Enterococcus* spp. harboring the VanA gene but retains in

vitro activity against Van B containing strains. Because VanA is the predominant gene circulating amongst *E. faecium* in the United States, telavancin should not be utilized empirically for the treatment of suspected VRE infections.

d. Oritavancin is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSIs) caused by *Enterococcus faecalis* (vancomycin-susceptible isolates only). The efficacy and safety has not been established in other infections such as bacteremia.
e. An increase in all-cause mortality has been observed across Phase 3 and 4 clinical trials in tigecycline-treated patients versus comparator-treated patients. In all 13 Phase 3 and 4 trials that included a comparator, death occurred in 4.0% (150/3788) of patients receiving tigecycline and 3.0% (110/3646) of patients receiving comparator drugs. In a pooled analysis of these trials, based on a random effects model by trial weight, an adjusted risk difference of all-cause mortality was 0.6% (95% CI 0.1, 1.2) between tigecycline and comparator-treated patients. The cause of this increase has not been established. This increase in all-cause mortality should be considered when selecting among treatment options.
f. Quinupristin-dalfopristin is not active against *E. faecalis.*

Dosage Recommendations for Intravenous Treatment of VRE Infections

	Dose
Linezolid	600mg IV every 12 hours
Quinupristin-dalfopristin	7.5mg/kg IV every 8 hours
Daptomycin	6mg/kg IV every 24 hours[a]
Tedizolid	200mg IV/PO every 24 hours[b]
Tigecycline	100mg IV Loading Dose, Followed by 50mg IV every 12 hours

a. Dosage recommendation based upon FDA-approved dosage regimen for bacteremia/right-sided endocarditis
b. Dosage recommendation based upon FDA-approved dosage regimen for acute bacterial skin and skin structure infections.

Methicillin-Resistant *Staphylococcus aureus*

Vancomycin (intravenous administration) is recommended as first-line therapy for empiric and documented MRSA infections that require parenteral administration. The consensus review for therapeutic monitoring of vancomycin in adult patients recommend vancomycin trough concentrations be maintained above 10 mcg/mL to avoid development of resistance (trough range of 10-15 mcg/mL for uncomplicated infections) and higher trough concentrations (15-20 mcg/mL) are recommended for certain serious infections such as bacteremia, endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia. These recommendations are based upon pharmacokinetic and pharmacodynamic principles of vancomycin and on retrospective analyses of clinical outcomes. Studies suggest that vancomycin displays reduced activity against MRSA with MICs at the high end of the susceptible range (i.e., 1.5 – 2.0 mcg/mL). As a result, clinicians should know the MIC of vancomycin for serious MRSA infections, especially if the response to therapy is poor. Because current susceptibility testing methods are unable to reliably distinguish MICs of 1 mcg/mL from MICs of 2 mcg/mL, the patient's clinical and microbiologic response should also be considered when making decisions regarding therapy. The IDSA Guidelines for MRSA Infections have indicated that vancomycin can be utilized when the MIC is ≤ 2 mcg/mL). If a patient has not shown clinical improvement with vancomycin and trough concentrations have been optimized despite adequate debridement and removal of other foci of infection, switching to an alternative anti-MRSA agent is advisable regardless of MIC. Selection of alternative anti-MRSA agent(s) should be based upon in vitro susceptibility, site of infection, patient-specific factors, and FDA-approved indications. In vitro studies have shown reduced susceptibility to daptomycin in vancomycin-intermediate *S. aureus* (VISA). It is hypothesized that the thickened cell-wall present in VISA strains

may impede daptomycin's ability to penetrate the cell wall. There are insufficient data available to assess the relative clinical effectiveness of any other antibiotics against infections due to VISA.

Alternatives to Vancomycin for persons who require parenteral therapy for one of the following infections:

Complicated skin or skin structure infections (cSSSI) secondary to MRSA	**FDA-approved indication:** Ceftaroline Dalbavancin Daptomycin Linezolid Oritavancin Tedizolid Telavancin[a] Tigecycline[b] **Limited to in vitro data and clinical experience:** Quinupristin-dalfopristin[c]	**Recommendation:** *Selection of specific agent(s) is dependent on multiple factors such as site of infection, co-morbidities, presence of polymicrobial infection*
MRSA nosocomial pneumonia[d,e,f,g]	**FDA-approved indication:** Linezolid[h] Telavancin[g]	**Recommendation:** Linezolid
MRSA community-associated pneumonia[d,e,i,j]	**Limited to in vitro data and clinical experience:** Linezolid[h.k]	**Recommendation:** Linezolid
MRSA bacteremia[l]/right-sided endocarditis	**FDA-approved indication:** Daptomycin[m]	**Recommendation:** Daptomycin
MRSA (Other site of infection, e.g., septic arthritis, osteomyelitis, surgical site infection).[n,o]	**Limited to in vitro data and clinical experience** Daptomycin[d] Linezolid Tigecycline[b] Quinupristin-dalfopristin	*Selection of specific agent(s) is dependent on multiple factors such as site of infection, co-morbidities, presence of polymicrobial infection*

a. In a subanalysis of pooled cSSSI studies, clinical cure rates in the telavancin treatment group were lower in patients with impaired renal function (CrCl< 50 ml/min) than compared to those with a CrCl>50 ml/min. Caution is advised in patients with renal impairment (CrCl < 50 mL/min).
b. An increase in all-cause mortality has been observed across Phase 3 and 4 clinical trials in tigecycline-treated patients versus comparator-treated patients. In all 13 Phase 3 and 4 trials that included a comparator, death occurred in 4.0% (150/3788) of patients receiving TYGACIL and 3.0% (110/3646) of patients receiving comparator drugs. In a pooled analysis of these trials, based on a random effects model by trial weight, an adjusted risk difference of all-cause mortality was 0.6% (95% CI 0.1, 1.2) between tigecycline and comparator-treated patients. The cause of this increase has not been established. Boxed warning states that tigecycline should be reserved for use in situations when alternative treatments are not suitable. Thus, this increase in all-cause mortality should be considered when selecting among treatment options. In addition, tigecyline is not indicated for the treatment of diabetic foot infections; clinical trial failed to demonstrate non-inferiority of tigecycline for treatment of diabetic foot infections.
c. Quinupristin-dalfopristin is FDA approved for treatment of cSSSI due to MSSA (not MRSA).

d. Daptomycin should not be used to treat pneumonia; daptomycin binds to surfactant which leads to sub-therapeutic concentrations at the site of infection.
e. Quinupristin-dalfopristin is not FDA approved to treat pneumonia nor is it approved to treat infections due to MRSA. It has been used to treat MRSA pneumonia in the clinical setting. In 38 evaluable patients, the cure rate was 31% and 44% for quinupristin-dalfopristin and vancomycin, respectively (Fagon 2000).
f. Tigecycline has not received FDA indication for treatment of hospital-associated pneumonia. In the Phase III clinical trial that randomized patients to tigecycline or imipenem, tigecycline did not meet noninferiority in one of the co-primary efficacy endpoints. Even though the study design allowed patients to receive adjunctive therapies, patients with ventilator-associated pneumonia experienced lower cure rates (47.9% versus 70.1% for the clinically evaluable population) and greater mortality (25/131 [19.1%] versus 14/122 [11.5%]) than the comparator regimen. High mortality rates were seen among tigecycline-treated patients with ventilator-associated pneumonia and bacteremia at baseline (9/18 [50.0%] versus 1/13 [7.7%] in comparator-treated patients). In this trial, the microbiological response rate in persons infected by MRSA was 12/27 (44.4%) for persons receiving tigecycline and 21/30 (70%) for persons receiving other antimicrobials.
g. Telavancin received FDA approval for hospital-acquired and ventilator-associated bacterial pneumonia (HABP/VABP) caused by susceptible isolates of *Staphylococcus aureus*. However, per PI, it should be reserved for use when alternative treatments are not suitable. A box warning states that patients with pre-existing moderate/severe renal impairment (CrCl ≤50 mL/min) who were treated with telavancin for HABP/VABP had increased mortality observed versus vancomycin; thus, use of telavancin in these patients should be considered only when the anticipated benefit to the patient outweighs the potential risk.
h. Linezolid is FDA approved for treatment of MRSA nosocomial pneumonia. Although retrospective analysis of 2 studies suggested superiority of linezolid to vancomycin (Wunderink 2003), these data require confirmation before linezolid can be recommended as first-line therapy for patients with MRSA pneumonia (Stevens 2002).
i. Tigecycline is FDA approved for treatment of community-acquired pneumonia caused by *Streptococcus pneumoniae* (penicillin susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and *Legionella pneumophila* (not MRSA).
j. Ceftaroline is FDA approved for treatment of community-acquired pneumonia caused by Gram-Positive and Gram-Negative organisms including *S. pneumoniae* with concurrent bacteremia, *S. aureus* (MSSA only), *H. influenza*, *K. pneumonia*, *K. oxytoca*, and *E. coli*. In the Phase III community-acquired pneumonia clinical trials, patients with known or suspected MRSA were excluded.
k. Linezolid is FDA approved for treatment of community-acquired pneumonia due to MSSA (not MRSA).
l. According to package insert (March 2007 revision), linezolid monotherapy should be avoided for the treatment of catheter-related bloodstream or catheter-site infections. Higher mortality was seen in patients treated with linezolid compared to vancomycin/dicloxacillin/oxacillin for intravascular catheter-related infections (21.5% vs 16%, OR=1.426 CI 0.970. 2.098). The differences were primarily in patients with Gram-negative, mixed Gram-negative and Gram-positive pathogens, or no baseline pathogens.
m. Presence of septic pulmonary emboli is not an exclusion for daptomycin; however, caution should be exercised as surfactant has been shown to inactivate daptomycin. In the endocarditis clinical trial, 10 daptomycin-treated patients with right-sided endocarditis had a septic pulmonary emboli; 6 of the 10 patients demonstrated success (3/6 patients with MSSA, 3/4 patients with MRSA) (Cubist Pharmaceuticals, Inc. Data on File).
n. Dalbavancin is only indicated for the treatment of adult patients with acute bacterial skin and skin structure infections. The efficacy and safety has not been established in other infections.

o. Oritavancin is only indicated for the treatment of adult patients with acute bacterial skin and skin structure infections. The efficacy and safety has not been established in other infections. In Phase 3 ABSSSI clinical trials, more cases of osteomyelitis were reported in the oritavancin-treated arm than in the vancomycin-treated arm. If osteomyelitis is suspected or diagnosed, institute appropriate alternate antibacterial therapy.

Dosage Recommendations for Intravenous Treatment of MRSA Infections

	Dose
Ceftaroline	600mg IV every 12 hours
Dalbavancin	1000mg IV infusion followed one week later by a 500 mg IV infusion Note: only approved for acute bacterial skin and skin structure infections
Daptomycin	Complicated skin and skin structure: 4mg/kg IV every 24 hours Bacteremia/rt-sided endocarditis: 6mg/kg IV every 24 hours
Linezolid	600mg IV every 12 hours
Oritavancin	Single 1200mg IV infusion over 3 hours Note: only approved for acute bacterial skin and skin structure infections
Quinupristin-dalfopristin	7.5mg/kg IV every 12 hours
Tedizolid	200mg IV every 24 hours
Telavancin	10 mg/kg IV q 24 hours
Tigecycline	100mg IV Loading Dose, Followed by 50mg IV every 12 hours
Vancomycin	15 mg/kg IV q 8-12 hours

IV to PO Switch for MRSA Infections

Patients being converted from IV to oral therapy for MRSA infections should be clinically stable and thus suitable for treatment with clindamycin, trimethoprim-sulfamethoxazole, doxycycline or minocycline if the isolate is shown to be susceptible to one of these agents. The susceptibility of MRSA to fluoroquinolones is highly variable; in many facilities over 90% of MRSA isolates are resistant to these agents. The use of fluoroquinolones should be avoided for treatment of MRSA infections unless susceptibility is well-documented. Occasional MRSA isolates may demonstrate susceptibility to moxifloxacin but not to other fluoroquinolones; however, moxifloxacin has not been shown to be effective in the treatment of such infections. Clindamycin should be used only after demonstration of in vitro susceptibility, including exclusion of macrolide (erythromycin)-inducible clindamycin resistance using the "D-test" or an acceptable alternative. Oral linezolid and tedizolid should be reserved for patients with serious MRSA infections for whom an oral route of administration is favored. According to the manufacturer, the maximum recommended duration of linezolid therapy is 28 days (calculated as total days of intravenous and oral); many of the linezolid-related toxicities are associated with prolonged therapy (>28 days). The recommended duration of tedizolid therapy is six days for skin infections. Long-term safety of tedizolid phosphate is currently unknown at this time.

TOXICITIES AND WARNINGS

Ceftaroline

Direct Coombs' test seroconversion has been reported with ceftaroline. Seroconversion from a negative to a positive direct Coombs' test result occurred in 120/1114 (10.8%) of patients receiving ceftaroline and 49/1116 (4.4%) of patients receiving comparator drugs in the four pooled Phase 3 trials. In the pooled

Phase 3 community-acquired bacterial pneumonia trials, 51/520 (9.8%) of ceftaroline-treated patients compared to 24/534 (4.5%) of ceftriaxone-treated patients seroconverted from a negative to a positive direct Coombs' test result. No adverse reactions representing hemolytic anemia were reported in any treatment group. If anemia develops during or after therapy with ceftaroline, drug-induced hemolytic anemia should be considered and an appropriate diagnostic workup, including a Coombs' test, commenced. Discontinuation of ceftaroline should be considered if hemolytic anemia is suspected.

Dalbavancin

Dalbavancin is a lipoglycopeptide with a prolonged half-life (~346 hours) that enables a unique two-dose regimen. Serious hypersensitivity (anaphylactic) and skin reactions have been reported with glycopeptides including dalbavancin. No data are available on cross-reactivity between dalbavancin and other glycopeptides, including vancomycin. In addition, rapid intravenous infusion can cause reactions similar to "red-man syndrome". In Phase 2 and 3 clinical trials, dalbavancin-treated group experienced more ALT elevation >3 times ULN compared to other treatment group.

Daptomycin

The manufacturer recommends that patients be monitored for muscle pain or weakness, particularly of the distal extremities and to obtain weekly CPK levels while on therapy. Patients developing unexplained CPK elevations should be monitored more frequently; however, those with substantially elevated CPK (≥ 10 X ULN) should discontinue daptomycin. Daptomycin should also be discontinued in those who have unexplained symptoms of myopathy and elevated CPK. It is suggested that HMG-CoA reductase inhibitors be temporarily discontinued while receiving daptomycin. The manufacturer updated the product information that decreased efficacy has been shown in patients with moderate baseline renal impairment from sub-group analysis of clinical trial data and recommends considering these data in the product information (refer to tables below) when selecting antibacterial therapy for use in patients with baseline moderate to severe renal impairment. In postmarketing surveillance, eosinophilic pneumonia has been reported in patients receiving daptomycin. In these cases, patients developed fever, dyspnea with hypoxic respiratory insufficiency, and diffuse pulmonary infiltrates. These patients typically developed eosinophilic pneumonia 2 to 4 weeks after starting daptomycin and improved when daptomycin was discontinued and steroid therapy was initiated. The recurrence of eosinophilic pneumonia with retreatment of daptomycin has been reported.

Table: Success Rates by Stratified by Creatinine Clearance in the Complicated Skin and Skin Structure Trial

	Success Rate in ITT population n/N (%)	
Clearance Clearance	Daptomycin 4mg/kg every 24 hours	Comparator
50 - 70 mL/min	25/38 (66%)	30/48 (63%)
30 - <50 mL/min	7/15 (47%)	20/35 (57%)

Table: Success Rates by Stratified by Creatinine Clearance in the Bacteremia/Endocarditis Trial

	Success Rate in ITT population n/N (%)			
	Daptomycin 6mg/kg every 24 hours		Comparator	
Creatinine Clearance	Bacteremia	Right-sided Infective Endocarditis	Bacteremia	Right-sided Infective Endocarditis
>80 mL/min	30/50 (60%)	7/14 (50%)	19/42 (45%)	5/11 (46%)
50 - 80 mL/min	12/26 (46%)	1/4 (25%)	13/31 (42%)	1 /2 (50%)

30 - 50 mL/min	2/14 (14%)	0/1 (0%)	7/17 (41%)	1/1 (100%)

Linezolid

Myelosuppression has been reported in patients receiving linezolid. Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with linezolid should be considered in patients who develop anemia, leukopenia, pancytopenia, or thrombocytopenia. Cases of peripheral and/or optic neuropathy have been reported with linezolid therapy; the manufacturer recommends monitoring visual function in all patients receiving linezolid greater than 3 months. Lactic acidosis is another adverse event that has been reported with linezolid therapy. It is hypothesized that the all of these toxicities (myelosuppression, neuropathy, and lactic acidosis) may be related to linezolid's ability to inhibit mitochondrial protein synthesis as a result of similarities between bacterial and mitochondrial ribosomes.

Linezolid is a reversible, nonselective inhibitor of monoamine oxidase and may interact with adrenergic and serotonergic agents. Cases of serotonin syndrome associated with co-administration of linezolid and serotonergic agents (e.g., selective serotonin reuptake inhibitors) have been reported. Meals with high tyramine content (>100mg per meal) should be avoided during linezolid therapy. Foods high in tyramine content include those that may have undergone protein changes by aging, fermentation, pickling or smoking to improve favor, such as aged cheeses (0 to 15mg tyramine per ounce), fermented or air-dried meats (0.1 to 8mg tyramine per ounce), tap beers (4mg tyramine per 12 ounces), red wine (0 to 6mgn tyramine per 8 ounces). In July 2011, FDA Drug Safety Communication published that serious CNS reactions are possible when linezolid is given to patients taking serotonergic psychiatric medications. The FDA Drug Safety Communication recommended the following:

-Linezolid should generally not be given to patients taking serotonergic drugs. However, there are some conditions that may be life-threatening or require urgent treatment with linezolid such as when:

- Linezolid is used to treat vancomycin-resistant *Enterococcus faecium* (VRE) infections.
- Linezolid is used to treat infections such as nosocomial pneumonia and complicated skin and skin structure infections, including cases caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

-In emergency situations requiring life-threatening or urgent treatment with linezolid (as described above), the availability of alternative interventions should be considered and the benefit of linezolid treatment should be weighed against the risk of serotonin toxicity. If linezolid must be administered to a patient receiving a serotonergic drug, the serotonergic drug must be immediately stopped and the patient should be closely monitored for emergent symptoms of CNS toxicity for two weeks (five weeks if fluoxetine was taken), or until 24 hours after the last dose of linezolid, whichever comes first.

-In non-emergency situations when non-urgent treatment with linezolid is contemplated and planned, the serotonergic psychiatric medication should be stopped, to allow its activity in the brain to dissipate. Most serotonergic psychiatric drugs should be stopped at least 2 weeks in advance of linezolid treatment. Fluoxetine, which has a longer half-life compared to similar drugs, should be stopped at least 5 weeks in advance.

-Treatment with the serotonergic psychiatric medication may be resumed 24 hours after the last dose of linezolid. Serotonergic psychiatric medications should not be started in a patient receiving linezolid. Wait until 24 hours after the last dose of linezolid before starting the antidepressant.

- Patients should be educated to recognize the symptoms of serotonin toxicity or CNS toxicity and advise them to contact a healthcare professional immediately if they experience any symptoms while taking serotonergic psychiatric medications or linezolid.

Oritavancin

Oritavancin is a lipoglycopeptide with a prolonged half-life (~245 hours) that enables a unique single dose regimen. Serious hypersensitivity reactions have been reported with oritavancin; there is a potential for cross-sensitivity in patients with previous reactions to glycopeptides. In the Phase 3 clinical trials, the median onset of hypersensitivity reactions was 1.2 days and the median duration of these reactions was 2.4 days. In addition, rapid intravenous infusion can cause reactions similar to "red-man syndrome". Oritavancin has no effect on the coagulation system; however, it has been shown to artificially prolong aPTT for up to 48 hours, and may prolong PT and INR for up to 24 hours. Oritavancin can bind and prevent the action of the phospholipid reagents which activate coagulation in commonly used laboratory coagulation tests. Thus, the prescribing information states the use of IV unfractionated heparin sodium is contraindicated for 48 hours after oritavancin administration. For patients who require aPTT monitoring within 48 hours of oritavancin dosing, a non-phospholipid dependent coagulation test such as a Factor Xa (chromogenic) assay or an alternative anticoagulant not requiring aPTT monitoring may be considered. Besides making the anticoagulation effect of warfarin unreliable up to 24 hrs after an oritavancin dose, the co-administration of oritavancin and warfarin may result in higher exposure of warfarin, which may increase the risk of bleeding. Drug interaction studies found oritavancin be a nonspecific weak inhibitor (CYP2C9 and CYP2C19) or inducer (CYP3A4 and CYP2D6) of several CYP isoforms. Thus, the prescribing information states that caution should be used when administering oritavancin concomitantly with drugs with a narrow therapeutic window that are predominantly metabolized by one of the affected CYP450 enzymes (e.g., warfarin). In Phase 3 clinical trials, more cases of osteomyelitis were reported in the oritavancin treated arm than in the vancomycin-treated arm. Monitor patients for signs and symptoms of osteomyelitis. If osteomyelitis is suspected or diagnosed, institute appropriate alternate antibacterial therapy.

Quinupristin-dalfopristin

Quinupristin-dalfopristin is a significant inhibitor of cytochrome P450 3A4. Co-administration of quinupristin-dalfopristin with drugs that are substrates of CYP 3A4 and possess a narrow therapeutic window requires caution and monitoring. Co-administration of medications metabolized by CYP 3A4 that prolong QTc interval should be avoided. Arthralgias and/or myalgias including severe cases have been reported in patients receiving this agent. Quinupristin-dalfopristin diluted in 250cc of D5W is administered by peripheral IV infusion. If moderate or severe venous irritation occurs, the infusion volume can be increased to 500 or 750cc or it can be administered via a central line or peripherally inserted central catheter (PICC).

Tedizolid

The warnings and precaution state that the safety and efficacy of tedizolid phosphate in patients with an ANC < 1000 cells/mm^3 has not been adequately evaluated and alternative treatments should be considered in patients with neutropenia. Tedizolid phosphate has been shown to be a reversible inhibitor of monoamine oxidase (MAO) *in vitro*, but no restrictions exist for concomitant use of drugs with adrenergic and serotonergic activity or tyramine containing foods according to the prescribing information.[1] Of note, patients taking such medications were excluded from Phase 2 and 3 trials. Phase III clinical studies demonstrated non-inferiority of 6 days of tedizolid phosphate vs 10 days of linezolid (FDA approved duration). Long-term safety of tedizolid phosphate is currently unknown at this time.

Telavancin

Telavancin is a semi-synthetic derivative of vancomycin; it is unknown if patients with hypersensitivity reactions to vancomycin will experience cross-reactivity to telavancin. Telavancin should be avoided in patients with known hypersensitivity to vancomycin. The prescribing information contains boxed warning for telavancin's fetal risk (ie, adverse developmental outcomes were shown in animal studies at

clinically relevant doses; pregnancy category C). The boxed warning states that the use of telavancin should be avoided during pregnancy unless potential benefit to the patient outweighs potential risk to the fetus. Women of childbearing potential should have serum pregnancy test prior to administration of telavancin and should use effective contraception during telavancin therapy (if pregnancy test results are negative). New onset or worsening renal impairment occurred in telavancin-treated patients; monitor renal function (i.e., serum creatinine, creatinine clearance) in all patients receiving telavancin. Values should be obtained prior to initiation of treatment, during treatment (at 48 to 72-hour intervals or more frequently, if clinically indicated), and at the end of therapy. Telavancin contains hydroxypropyl-beta-cyclodextrin, which is excreted in urine and may accumulate in patients with renal impairment. Serum creatinine should be closely monitored and, if renal toxicity is suspected, an alternative agent should be considered. Similar to vancomycin, telavancin should be infused over 60 minutes; rapid infusion may be associated with infusion related reactions including flushing of the upper body, urticaria, pruritus, or rash. In a study involving healthy volunteers, telavancin prolonged the QTc interval. Caution is warranted when prescribing telavancin to patients taking drugs known to prolong the QT interval. Use of telavancin should be avoided in patients with congenital long QT syndrome, known prolongation of the QTc interval, uncompensated heart failure, or severe left ventricular hypertrophy. Patients with these conditions were not included in clinical trials of telavancin. Telavancin does not interfere with coagulation; however, it interferes with certain tests (i.e., prothrombin time, international normalized ratio, activated partial thromboplastin time, activated clotting time, and coagulation based factor Xa tests) used to monitor coagulation when these samples are drawn 0 to 18 hours after telavancin administration for patients being treated once every 24 hours. Because of this, intravenous unfractionated heparin sodium is contraindicated with telavancin. For patients who require aPTT monitoring, a non phospholipid dependent coagulation test such as Factor Xa (chromogenic) assay; refer to PI for additional details. Blood samples for these other coagulation tests affected by telavancin should be collected as close as possible prior to a patient's next dose of telavancin.

Tigecycline

In the clinical trial for cSSSI, nausea and vomiting was reported 35.0% and 20.0% in patients receiving tigecycline compared to 8.9% and 4.2% of those receiving vancomycin/aztreonam, respectively. The administration of tigecycline in the fed state may improve the tolerability; extending the infusion was not shown to impact tolerability. Tigecycline is listed as Pregnancy Category D; administration during pregnancy may cause fetal harm. Similar to tetracyclines, tigecycline may cause permanent tooth discoloration when administered to children less than 8 years old or pregnant woman (i.e., last half of pregnancy). Hepatic dysfunction and liver failure have been reported with tigecycline; providers should monitor liver function. Tigecycline should be used cautiously in patients with baseline severe hepatic impairment (Child Pugh C); these patients should receive dosage reduction and be closely monitored for hepatic and clinical response. Acute pancreatitis, including fatal cases, has occurred in association with tigecycline treatment. Providers should consider the diagnosis of acute pancreatitis in patients who develop clinical symptoms, signs, or laboratory abnormalities suggestive of acute pancreatitis and should consider discontinuation of tigecycline in these patients.

An increase in all-cause mortality has been observed across Phase 3 and 4 clinical trials in tigecycline-treated patients versus comparator-treated patients. The pooled analysis grouped 13 trials with patients given tigecycline for both approved and unapproved indications by type of infection (refer to Table below), comparing the overall mortality for tigecycline versus pooled control agents. Overall, in the trials, death occurred in 4.0% (150/3788) of patients receiving tigecycline and 3.0% (110/3646) of patients receiving comparator antibiotics. An adjusted risk difference for all-cause mortality based on a random effects model stratified by trial weight was 0.6% (95% CI 0.1, 1.2) between tigecycline and comparator treated patients. Based upon these all-cause mortality results, a boxed warning states that tigecycline should be reserved for use in situation when alternative treatments are not suitable.

Table: FDA Analyses of Patients with outcome of death by infection type

Infection Type	Tigecycline deaths/ total patients (%)	Comparator Antibiotics deaths/ total patients (%)	Risk Difference (95% Confidence Interval)
Complicated skin and skin structure infection	12/834 (1.4%)	6/813 (0.7%)	0.7 (-0.3, 1.7)
Complicated intra-abdominal infections	42/1382 (3.0%)	31/1393 (2.2%)	0.8 (-0.4, 2.0)
Community-acquired pneumonia	12/424 (2.8%)	11/422 (2.6%)	0.2 (-2.0, 2.4)
Hospital-acquired pneumonia	66/467 (14.1%)	57/467 (12.2%)	1.9 (-2.4, 6.3)
Non-Ventilator-associated pneumonia (subset of hospital-acquired patients)	41/336 (12.2%)	42/345 (12.2%)	0.0 (-4.9, 4.9)
Ventilator-associated pneumonia (subset of hospital-acquired patients)	25/131 (19.1%)	15/122 (12.3%)	6.8 (-2.1, 15.7)
Resistant pathogens	11/128 (8.6%)	2/43 (4.7%)	3.9 (-4.0, 11.9)
Diabetic foot infection	7/553 (1.3%)	3/508 (0.6%)	0.7 (-0.5, 1.8)
Overall Adjusted	150/3788 (4.0%)	110/3646 (3.0%)	0.6 (0.1, 1.2)

REFERENCES

Vancomycin-resistant enterococcus

Krause KM, Renelli M, Difuntorum S, et al. In vitro activity of telavancin against resistant Gram-positive bacteria. Antimicrob Agents Chemother 2008; 52: 2647-2652.

Rubinstein E and Keynan Y. Vancomycin-resistant enterococci. Crit Care Clin. 2013;29:841-52.

Sahm D, Deane J, Bien P, et al. Results of the Surveillance of Tedizolid Activity and Resistance Program: In vitro susceptibility of Gram-positive pathogens collected in 2011 and 2012 from the United States and Europe. Diagnostic Microbiology and Infectious Disease 2015;81:112-118.

cSSSI trials

Arbeit RD, Maki D, Tally FP, et al. The safety and efficacy of daptomycin for the treatment of complicated skin and skin-structure infections. Clin Infect Dis 2004;38:1673-81.

Breedt J, Teras J, Gardovskis J, et al. Safety and efficacy of tigecycline in treatment of skin and skin structure infections: results of a double-blind phase 3 comparison study with vancomycin-aztreonam. Antimicrob Agents Chemother 2005;49:4658-66.

Boucher HW, Wilcox M, Talbot GH et al. Once-weekly dalbavancin versus daily conventional therapy for skin infection. N Engl J Med. 2014 Jun 5; 370(23): 2169-79

Corey GR, Kabler H, Mehra P, et al. Single-dose oritavancin in the treatment of acute bacterial skin infections. N Engl J Med. 2014 June 5;370(23):2180-2190.

Corey GR, Good S, Jiang H, et al. Single-dose oritavancin versus 7-10 days of vancomycin in the treatment of gram-positive acute bacterial skin and skin structure infections: The SOLO II noninferiority study. Clin Infect Dis 2015 January 15;60(2):254-262

Moran G, Fang E, Corey G, et al. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomized, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis 2014;14:696-705.

Nichols RL, Graham DR, Barriere SL, et al. Treatment of hospitalized patients with complicated gram-positive skin and skin structure infections: two randomized, multicenter studies of quinupristin/dalfopristin versus cefazolin, oxacillin or vancomycin. J Antimicrob Chemother 1999; 44: 263-273.

Prokocimer P, De Anda C, Fang E, et al. Tedizolid Phosphate vs Linezolid for Treatment of Acute Bacterial Skin and Skin Structure Infections: The ESTABLISH-1 Randomized Trial. JAMA 2013;309(6):559-69.

Stryjewski M, Graham, DR, Wilson, SE, O'Riordan, et al. Telavancin versus Vancomycin for the Treatment of Complicated Skin and Skin-Structure Infections Caused by Gram-Positive Organisms. Clin Infect Dis 2008;46:1683-93.

Weigelt J, Itani K, Stevens D, et al. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. Antimicrob Agents Chemother 2005;49:2260-6.

Methicillin-resistant staphylococcus

Cui L, Tominaga E, Neoh H, Hiramatsu K. Correlation between reduced daptomycin susceptibility and vancomycin resistance in vancomycin-intermediate *Staphylococcus aureus*. Antimicrob Agents Chemother 2006;50:1079-1082.

Howden BP, Ward PB, Charles PGP, et al. Treatment outcomes for serious infections caused by methicillin-resistant *Staphylococcus aureus* with reduced vancomycin susceptibility. Clin Infect Dis 2004; 38: 521-528.

Sakoulas G, Thauvin-Eliopoulus C, Moellering RC Jr., Eliopoulos GM. Induction of daptomycin heterogeneous susceptibility in *Staphylococcus aureus* by exposure to vancomycin. Antimicrob Agents Chemother 2006;50:1581-1585.

Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC Jr, Eliopoulus GM. Relationship of MIC bactericidal activity to efficacy of vancomycin treatment of methicillin-resistant Staphylococcus aureus bacteremia. J Clin Microbiol 2004;42:2398-402.

Stevens DL, Herr D, Lampiris H, et al. Linezolid versus vancomycin for the treatment of methicillin-resistant staphylococcus aureus infections. Clin Infect Dis 2002; 34: 1481-1490.

Trzcinski K, Cooper BS, Hryniewicz W, Dowson CG. Expression of resistance to tetracyclines in strains of methicillin-resistant Staphylococcus aureus. J Antimicrob Chemother 2000;45:763-70.

Other

American Thoracic Society, Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med 2005;171:388-416.

Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America. Circulation 2005;111:e394-434.

Draghi DC, Benton BM, Krause KM, et al. Comparative Surveillance Study of Telavancin Activity against Recently Collected Gram-Positive Clinical Isolates across the United States. Antimicrob Agents Chemother. 2008;52:2383-88.

FDA Drug Safety Communication: Increased risk of death with Tygacil (tigecycline) compared to other antibiotics used to treat similar infections. Available at http://www.fda.gov/Drugs/DrugSafety/ucm224370.htm#ds Accessed Dec 28, 2010.

FDA Drug Safety Communication: Serious CNS reactions possible when linezolid (Zyvox) is given to patients taking certain psychiatric medications. Available at http://www.fda.gov/Drugs/DrugSafety/ucm265305.htm#hcp Accessed September 4, 2011.

Jeffres MN, Isakow W, Doherty JA, et al. Predictors of mortality for methicillin-resistant *Staphylococcus aureus* health-care-associated pneumonia; specific evaluation of vancomycin pharmacokinetic indices. Chest 2006;130:947-55.

Jones RN, Sader HS, Flamm RK. Update of dalbavancin spectrum and potency in the USA: report from the SENTRY Antimicrobial Surveillance Program (2011). Diagnostic Microbiology and Infectious Disease. 2013;75:304-307

Liu C. Clinical Practice Guidelines by the Infectious Diseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus Aureus Infections in Adults and Children. CID 2011:52 (on-line access January 4, 2011).

Mendes RE, Farrell DJ, Sader HS, et al. Activity of oritavancin against gram-positive clinical isolates responsible for documented skin and soft-tissue infections in European and US hospitals (2010-13). J Antimicrob Chemother. 2015;70:498-504.

Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of ASHP, IDSA, and SIDP. Am J Health-Syst Pharm. 2009; 66:82-98.

Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft tissue infections: 2014 update by the Infectious Diseases Society of America. Clin Infect Dis. 2014;59 (2): 147-159

Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice Guidelines for the management of bacterial meningitis. Clin Infect Dis 2004;39:1267-84.

Prescribing Information

Cubicin [package insert]. Lexington, MA: Cubist Pharmaceuticals, Inc; November 2010.

Dalvance [package insert]. Chicago, IL: Durata Therapeutics Inc; 2014.

ORBACTIV [package insert]. The Medicines Company, Parsippany, NJ; September 2014.

Sivextro [package insert]. Lexington, MA: Cubist Pharmaceuticals, Inc. June 2014.

Synercid [package insert]. Greenville, NC: DSM Pharmaceuticals, Inc; June 2008.

Teflaro [package insert]. St. Louis, MOForest Pharmaceuticals, Inc.; January 2011

Tygacil [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals, Inc; September 2013.

Vibativ [package insert]. South San Francisco, CA: Theravance Inc; November 2014.

Zyvox [package insert]. NY, NY: Pfizer, Inc; June 2008.

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