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## New intravenous antibiotics: a focused pharmacotherapy update

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# New intravenous antibiotics: a focused pharmacotherapy update

## **Abstract**

Infections due to multidrug-resistant pathogens are increasing throughout the world, in particular due to the emergence of resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus (VRE) penicillin-resistant *Streptococcus pneumonia*, multidrug-resistant (MDR) *Pseudomonas* and *Acinetobacter* spp, extended-spectrum  $\beta$ -lactamase- (ESBL) producing enteric organisms, etc. These serious pathogens are a major cause of severe hospital and community-acquired infections and are associated with high morbidity and mortality. Several new parenteral antibiotics have been approved in the past several years to help treat these infections, including telavancin, doripenem, tigecycline and daptomycin. This article reviews the pharmacology and limitations of these new antibiotics in treating infections in adult critically ill patients. Despite these advances however, antibiotic research and development continues to be vital in treating infections caused by resistant organisms and addressing current and emerging clinical challenges.<sup>1-3</sup>

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**ANTIINFECTIVE COLUMN**

**New Intravenous Antibiotics: A Focused Pharmacotherapy Update**

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Infections due to multidrug-resistant pathogens are increasing throughout the world, in particular due to the emergence of resistant *Staphylococcus aureus*, vancomycin-resistant enterococcus (VRE) penicillin-resistant *Streptococcus pneumoniae*, multidrug-resistant (MDR) *Pseudomonas* and *Acinetobacter* spp, extended-spectrum  $\beta$ -lactamase- (ESBL) producing enteric organisms, etc. These serious pathogens are a major cause of severe hospital and community-acquired infections and are associated with high morbidity and mortality. Several new parenteral antibiotics have been approved in the past several years to help treat these infections, including telavancin, doripenem, tigecycline and daptomycin. This article reviews the pharmacology and limitations of these new antibiotics in treating infections in adult critically ill patients. Despite these advances however, antibiotic research and development continues to be vital in treating infections caused by resistant organisms and addressing current and emerging clinical challenges.<sup>1-3</sup>

### *Telavancin*

Telavancin, US brand name Vibativ™, is a novel bactericidal lipoglycopeptide antibiotic and a synthetic derivative of vancomycin. Telavancin was FDA-approved in September 2009.

### **Indications and Place in Therapy**

Telavancin is currently approved to treat complicated skin and skin structure infections caused by susceptible gram-positive organisms.<sup>4</sup>

Telavancin demonstrates enhanced activity in vitro against methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae*, glycopeptides-

intermediate *S. aureus* and Van A-type enterococci. This agent may become an important therapeutic option in treating serious infections from resistant gram-positive cocci, particularly those caused by MRSA.<sup>3</sup> This may be especially true when considering the limitations, resistance and toxicity of other currently available gram-positive agents, including vancomycin, linezolid, daptomycin and tigecycline. The role of telavancin in clinical practice will become further elucidated as more data emerges for treating additional types of infections.

### **Spectrum and Mechanism of Action**

Telavancin has activity against a wide variety of gram-positive bacteria, including MRSA, vancomycin-susceptible *Enterococcus faecalis*, *Streptococcus pyogenes*, *Streptococcus agalactiae* and *Streptococcus anginosus*.<sup>4,5</sup>

Like vancomycin, telavancin acts by inhibiting cell wall synthesis by interfering with the polymerization and cross-linking of peptidoglycan and disrupts bacterial membrane barrier function, which results in a rapid bactericidal effect.<sup>3,4</sup>

### **Pharmacokinetics and Administration & Monitoring**

Telavancin is approximately 90% protein bound and has a serum half-life of approximately 8 hours. Telavancin also has a prolonged postantibiotic effect, lasting up to 6 hours, which allows for once-daily administration. Telavancin is primarily eliminated renally and requires dose adjustment in renal insufficiency.

The usual dose of telavancin is 10 mg/kg once a day, infused over 1 hour. The recommended duration of therapy is 7-14 days. Dose reduction is required for patients with creatinine clearances (CrCl) of less than 50 mL/min<sup>4</sup>: For CrCl of 30-50 mL/min, 7.5mg/kg

telavancin should be administered every 24 hours, and for CrCl of 10-29 mL/min, 10mg/kg telavancin should be administered every 48 hours. Unlike vancomycin, there are currently no recommendations for monitoring serum concentrations of telavancin.

## **Safety**

Telavancin may cause taste disturbances, nausea and vomiting; reversible increases in serum creatinine, QTc prolongation or foamy urine.<sup>4</sup> Also of note, the solubilizer that is used as an ingredient in telavancin, hydroxypropyl-beta-cyclodextrin, may accumulate in patients with renal dysfunction. Furthermore, as with vancomycin, infusing telavancin too quickly may cause “red man syndrome.”

Telavancin does not currently appear to have any relevant drug interactions; however it should be used cautiously with other agents that may prolong the QTc interval.

Of note, telavancin carries a Black Box Warning due to its potential for fetal toxicity. Women should have a pregnancy test prior to administration, and use of telavancin during pregnancy should be avoided if possible due to adverse outcomes observed in animal models. Furthermore, clinicians should consider switching to an alternative antibiotic if renal function is adversely affected by telavancin. Also, this agent should be avoided in patients at high risk for QTc prolongation.

## **Additional Notes**

Telavancin may cause falsely elevated coagulation parameters but does not affect actual coagulation. This is due to binding of a reagent used in anticoagulation testing. To minimize this interaction, blood samples for these tests should be collected immediately prior to telavancin

administration, when blood levels of telavancin are theoretically at their lowest. Also, it is important to be aware that Vibativ™ could potentially be confused with Viactiv®, Vibra-Tabs®, Vibramycin® or vigabatrin. Last, a telavancin Medication Guide is available from the manufacturer for distribution, which may be a valuable resource to provide for patients and caregivers: <http://www.astellas.us/docs/us/VIBATIV%20Med%20Guide%20Final.pdf><sup>6</sup>

### *Doripenem*

Doripenem (Doribax®) is the newest carbapenem and received initial U.S. approval in 2007.

### **Indications and Place in Therapy**

Doripenem is used for the treatment of complicated intra-abdominal infections and complicated urinary tract infections, including pyelonephritis, caused by susceptible gram-positive and gram-negative bacteria.<sup>7</sup>

Doripenem, like other carbapenems, will be used primarily to treat infections caused by MDR gram-negative pathogens, and its clinical use will likely be similar to that of meropenem.<sup>1</sup>

Decisions regarding formulary inclusion of doripenem will probably be largely based on cost.

### **Spectrum and Mechanism of Action**

Doripenem has a spectrum of activity similar to that of imipenem/cilastatin and meropenem<sup>8</sup> and is effective in treating both gram-negative and gram-positive pathogens, including *Pseudomonas aeruginosa* and anaerobes.<sup>9</sup>

Doripenem is a bactericidal agent that inhibits bacterial cell wall synthesis and subsequently causes cell death.

### **Pharmacokinetics and Administration & Monitoring**

Doripenem has a large volume of distribution and a half-life of approximately 1 hour. It is primarily eliminated renally and requires dose adjustment in renal insufficiency.

The usual dose of doripenem is 500 mg every 8 hours administered over one hour. Renal dose adjustment is required if CrCl is  $\leq 50$  mL/min.<sup>7</sup>: For CrCl of 30-50 mL/min, 250mg doripenem should be administered every 8 hours, and for CrCl of 11-29 mL/min, 250mg doripenem should be administered every 12 hours.

### **Safety**

Doripenem is well-tolerated, and the most common adverse effects include headache, nausea, diarrhea, rash and phlebitis.

Similar to other carbapenems, doripenem can reduce the serum concentrations of valproic acid, and concomitant use should be avoided if possible, as patients with seizure disorders will thus be at an increased risk for seizure activity. Also, co-administration of probenecid with doripenem may result in increased plasma concentrations of doripenem.<sup>7</sup>

Doripenem is contraindicated in patients with known hypersensitivity to doripenem or other carbapenems.



### *Tigecycline*

Tigecycline (Tygacil®) is a novel agent in a new class of antimicrobials known as the glycyclines, which are structurally related to tetracyclines.<sup>10</sup> Tigecycline was developed to overcome tetracycline resistance mediated by efflux pumps and ribosomal protection mechanisms. This agent was FDA-approved in 2005.<sup>3</sup>

Tigecycline's broad spectrum of activity provides another option for empiric therapy when treating serious infections, especially in cases of resistant organisms or when other agents are not expected to be effective. Tigecycline may also be administered as a single broad spectrum agent, which is helpful to simplify regimens in appropriate clinical situations, as an alternative to administering multiple agents targeting different pathogens. Drug pricing will likely influence hospital formulary inclusion of this agent.

### **Indications and Place in Therapy**

Tigecycline is indicated for the treatments of complicated skin and skin structure infections, complicated intra-abdominal infections and community-acquired bacterial pneumonia.<sup>11</sup>

### **Spectrum and Mechanism of Action**

Tigecycline possesses broad coverage against gram-negative and gram-positive pathogens, including MRSA, VRE, some ESBL-producing Enterobacteriaceae and anaerobes. However, it is important to note that tigecycline has poor activity against *Pseudomonas* and *Proteus* spp.<sup>10,12</sup>

Tigecycline is a bacteriostatic agent that, like other tetracycline derivatives, acts by inhibiting the 30S ribosomal subunit and thus protein synthesis. However, this agent is able to evade major mechanisms of tetracycline resistance.<sup>10</sup>

### **Pharmacokinetics and Administration & Monitoring**

Tigecycline has a complicated pharmacokinetic profile. It is quickly distributed and demonstrates extensive tissue penetration, producing high tissue concentrations outside of the bloodstream. Thus, due to its large volume of distribution, there is concern for using this agent to treat bloodstream infections, which warrants consideration by clinicians in cases of suspected or proven bacteremia.<sup>3,10</sup>

The usual dose of tigecycline is 100 mg once, followed by 50 mg every 12 hours. Doses are administered over approximately 30 to 60 minutes. Dosage adjustment is required in severe hepatic impairment (Child Pugh C), with an initial dose of 100 mg once followed by 25 mg every 12 hours.<sup>11</sup>

### **Safety**

The most common adverse reactions during tigecycline therapy include nausea, vomiting, diarrhea, abdominal pain, headache and increased liver enzymes.

Tigecycline may decrease oral contraceptive effectiveness and an additional form of birth control should be used during therapy. Tigecycline may also increase warfarin exposure and anticoagulation tests should be monitored closely if these agents are co-administered.<sup>11</sup>

### *Daptomycin*

Daptomycin (Cubicin®) is a cyclic lipopeptide, and the first of a new class of antimicrobial agents used to treat resistant gram-positive infections. Daptomycin received FDA approval in 2003.

### **Indications and Place in Therapy**

Daptomycin is indicated to treat complicated skin and skin structure infections and *Staphylococcus aureus* bacteremias, including those with right-sided infective endocarditis.<sup>13</sup> Daptomycin has also been effective in treating a variety of other infections. However, it is important to remember that this agent is inactivated by pulmonary surfactant and is thus not effective in treating pneumonia and other pulmonary infections.<sup>2,10</sup>

### **Spectrum and Mechanism of Action**

Daptomycin only has activity against gram-positive organisms, including MRSA, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae* subspecies *equisimilis* and vancomycin-susceptible *Enterococcus faecalis*.<sup>13</sup>

Daptomycin is a bactericidal agent with a unique mechanism of action. This agent disrupts the functional integrity of the bacterial plasma membrane, which results in rapid loss of membrane potential, cessation of macromolecular synthesis and cell death.<sup>3</sup>

### **Pharmacokinetics and Administration & Monitoring**

Daptomycin has a relatively long half-life of 8-9 hours in normal renal function and demonstrates a fairly prolonged post-antibiotic effect. Its pharmacokinetic properties conveniently allow for once-daily administration.

Daptomycin is usually dosed at 6-8mg/kg in critically ill patients, although doses of up to 12 mg/kg are well-tolerated and may be used in more difficult infections. Daptomycin is usually administered over 30 minutes.

### **Safety**

Daptomycin therapy is generally well-tolerated, however, due to the potential for myopathy, serum creatine kinase (CK) levels should be monitored at baseline and weekly thereafter during therapy. If possible, patients should also be monitored for symptoms of muscle pain. Daptomycin should be discontinued in patients with unexplained muscle pain or weakness with elevated CK levels or in asymptomatic patients who have markedly elevated CK (> 10 times the upper limit of normal).<sup>13</sup>

Experience with concomitant administration of daptomycin and warfarin is limited, therefore anticoagulant activity in patients receiving both agents should be monitored for the first several days of co-administration. Furthermore, daptomycin may falsely prolong warfarin anticoagulation parameters. This interaction can be minimized by drawing these labs at the time of daptomycin plasma trough concentrations, which is immediately prior to the next dose. Experience with co-administration of HMG-CoA reductase inhibitors and daptomycin is also limited, thus the temporary discontinuation of HMG-CoA reductase inhibitors should be considered in patients receiving daptomycin, due to the concern for myopathy.<sup>13</sup>

### **Additional Notes**

From a medication safety standpoint, clinicians should be aware that Cubicin® may be confused with Cleocin®.

### **Conclusion**

MDR pathogens have emerged over the past decade causing serious infections in ICU patients. Several new parenteral antibiotics have been introduced that demonstrate efficacy in overcoming resistance to these organisms, including telavancin, doripenem, tigecycline and daptomycin. However, these novel agents all have limitations and the potential to develop resistance; therefore, there is a continued need for investigational agents. Furthermore, it is important to remember that with these novel agents, as with all antibiotics, therapy should only be initiated when infections are proven or suspected, and should be modified as appropriate when culture and sensitivity data become available. This will help ensure that these antibiotics are being used appropriately now and will preserve their utility for future patients.

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